Connecting via Winsock to STN

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FILE 'HOME' ENTERED AT 11:12:36 ON 21 MAR 2007

=> file reg

=> s mefloquine/cn
L1            1 MEFLOQUINE/CN

=> s aroyltartaric acid
              0 AROYLTARTARIC
        8157667 ACID
L2            0 AROYLTARTARIC ACID
                  (AROYLTARTARIC(W)ACID)

=> s arsyltartaric acid
              0 ARSYLTARTARIC
        8157667 ACID
L3            0 ARSYLTARTARIC ACID
                  (ARSYLTARTARIC(W)ACID)

=> s arsyl tartaric acid
            311 ARSYL
           1449 TARTARIC
        8157667 ACID
L4            0 ARSYL TARTARIC ACID
                  (ARSYL(W)TARTARIC(W)ACID)

=> s threo-mefloquine/cn
L5            0 THREO-MEFLOQUINE/CN

=> s mefloquine
L6           13 MEFLOQUINE

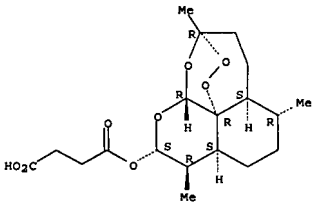
=> d
```

L6 ANSWER 1 OF 13 REGISTRY COPYRIGHT 2007 ACS on STN
RN 868128-13-6 REGISTRY
ED Entered STN: 16 Nov 2005
CN Butanedioic acid, mono[(3R,5aS,6R,8aS,9R,10S,12R,12aR)-decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl] ester, compd. with (αS)-α-(2R)-2-piperidinyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol (1:1) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Artesunate mefloquine salt
CN Mefloquine artesunate
FS STEREOSEARCH
MF C19 H28 O8 . C17 H16 F6 N2 O
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

CM 1

CRN 88495-63-0
CMF C19 H28 O8

Absolute stereochemistry. Rotation (+).

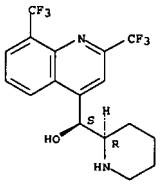


CM 2

CRN 51742-87-1
CMF C17 H16 F6 N2 O

Absolute stereochemistry. Rotation (+).

L6 ANSWER 1 OF 13 REGISTRY COPYRIGHT 2007 ACS on STN (Continued)



4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

```
=> file ca


=> s l1 or mefloquine
           953 L1
          1175 MEFLOQUINE
L7        1202 L1 OR MEFLOQUINE

=> s optical purity
        833455 OPTICAL
        168111 PURITY
L8        5110 OPTICAL PURITY
                 (OPTICAL(W)PURITY)

=> s l7 and l8
L9           3 L7 AND L8

=> s l7 and resolv?
        188693 RESOLV?
L10        15 L7 AND RESOLV?

=> s l7 and tartaric?
         37012 TARTARIC?
L11          3 L7 AND TARTARIC?

=> s l7 and ?tartaric?
         38436 ?TARTARIC?
L12          3 L7 AND ?TARTARIC?

=> s threomefloquine
L13          0 THREOMEFLOQUINE

=> s threo-mefloquine
         10672 THREO
          1175 MEFLOQUINE
L14          4 THREO-MEFLOQUINE
                 (THREO(W)MEFLOQUINE)

=> s erythro-mefloquine
         13336 ERYTHRO
          1175 MEFLOQUINE
L15         10 ERYTHRO-MEFLOQUINE
                 (ERYTHRO(W)MEFLOQUINE)

=> s l7 and (chiral or achiral)
        105841 CHIRAL
          5143 ACHIRAL
L16         40 L7 AND (CHIRAL OR ACHIRAL)

=> d l16 ibib abs
```

L16 ANSWER 1 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 146:175612 CA
TITLE: δ-Cyclodextrin as novel chiral probe for enantiomeric separation by electromigration methods
AUTHOR(S): Wistuba, Dorothee; Bogdanski, Anja; Larsen, Kim L.; Schurig, Volker
CORPORATE SOURCE: Institute of Organic Chemistry, University of Tuebingen, Tuebingen, Germany
SOURCE: Electrophoresis (2006), 27(21), 4359-4363
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Native δ-CD was employed as chiral selector in CE and MEKC. To study the potential of the enantiodiscriminating properties of δ-CD, neg. charged 5-dimethylamino-1-naphthalene-sulfonyl (dansyl)-, 2,4-dinitrophenyl (DNP)- and FMOC-derivs. of several amino acids, , flava-nones and three pos. charged drugs were selected as testing samples. Enantioresoln. factors up to 4.82 were observed The results were compared with those achieved by the conventional running buffer additives α-, β- and γ-CDs. For several examples a steady increase of enantioresoln. with increasing degree of oligomerization was detected.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l16 ibib abs 2-40

L16 ANSWER 2 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 144:323801 CA
TITLE: Monolithic silica-based capillary column with strong chiral cation-exchange type surface modification for enantioselective non-aqueous capillary electrochromatography
AUTHOR(S): Preinerstorfer, Beatrix; Lubda, Dieter; Lindner, Wolfgang; Laemmerhofer, Michael
CORPORATE SOURCE: Christian Doppler Laboratory for Molecular Recognition
Materials, Department of Analytical and Food Chemistry, University of Vienna, Vienna, A-1090, Austria
SOURCE: Journal of Chromatography, A [illegible] 1106(1-2), 94-105
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A silica-based monolithic stationary phase prepared by the sol-gel process in a 100 μm I.D. fused-silica (FS) capillary was modified chemical with 3-mercaptopropyl trimethoxysilane followed by immobilization of a strong cation-exchange (SCX) type chiral selector, (S)-N-(4-allyloxy-3,5-dichlorobenzoyl)-2-amino-3,3-dimethylbutane phosphonic acid, by radical addition reaction onto the reactive sulfhydryl surface. After a fine-tuning of the mobile phase composition, the enantioselective capillary column was evaluated for the separation of various chiral basic drugs by enantioselective nonaq. capillary electrochromatog. (CEC), in comparison to capillary column analogs packed with 3.5 μm silica particles having attached the same selector. The performance of the monolithic silica column was further compared to corresponding polymethacrylate-based organic polymer monoliths. Strong counterions such as 2-aminobutanol or N,N,N',N'-tetramethylethylenediamine are needed, although they reduce the electroosmotic flow velocity and separation factors in comparison to less efficient counterions, to allow the elution of the oppositely charged solutes in the ion-exchange retention mode within reasonable run time and as sharp zones. In contrast, weak counterions such as N,N-diisopropylethylamine (Huenig base) provided stronger electroosmotic flow and much better separation factors, but relatively poor peak efficiencies. Overall, with the chemical functionalized monolithic silica column the high quality sepns. of packed column analogs could be approximated, with regards to both separation factors and peak performances. However, the monolithic capillary column certainly outperformed the packed column in terms of system robustness under capillary electrochromatog. conditions and showed excellent column longevity. The enantioselective strong cation-exchange-type monolithic silica column performed also well in comparison to the organic polymer monolith.
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:278297 CA
TITLE: Chiral liquid chromatographic determination of mirtazapine in human plasma using two-phase liquid-phase microextraction for sample preparation
AUTHOR(S): Malagueno de Santana, Fernando Jose; Moraes de Oliveira, Anderson Rodrigo; Bonato, Pierina Sueli
CORPORATE SOURCE: Faculdade de Ciencias Farmaceuticas de Ribeirao Preto, Universidade de Sao Paulo, Ribeirao Preto, SP, Brazil
SOURCE: Analytica Chimica Acta [illegible] 549(1-2), 96-103
CODEN: ACACAM; ISSN: 0003-2670
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A simple, inexpensive and efficient preconcn. and clean-up liquid-phase microextn. method (LPME) using porous polypropylene hollow fiber membrane was developed for the extraction of the antidepressant mirtazapine from human plasma. The effects of different parameters influencing the efficiency of extraction were described and optimized. Under optimized conditions, mirtazapine was extracted with 22 μl toluene from 0.7 mL of plasma previously diluted with 3.1 mL deionized water and alkalinized with 0.15 mL 10 M NaOH. Mefloquine was used as internal standard The chromatog. anal. was carried out through chiral liquid chromatog. (LC) using a Chiralpak AD column and hexane-ethanol (98:2, volume/volume) plus 0.1% diethylamine as mobile phase, at a flow rate of 1.5 mL min-1. Detection was carried out at 292 nm. The mean recoveries of (+)-(S)- and (-)-(R)-mirtazapine were 29.1 and 28.8%, resp. The quantification limit (LOQ) was 6.25 ng ml-1 with linear response over the 6.25-625 ng ml-1 concentration range for both enantiomers. Within-day and between-day assay precision and accuracy were studied at three concentration levels (15, 100 and 500 ng ml-1). For both mirtazapine enantiomers, the coeffs. of variation (CV) and deviation from the theor. values were lower than 15% at all concentration levels. The developed and validated method showed that LPME is a promising technique for sample preparation for the analyses of chiral drugs in biol. samples.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:185864 CA
TITLE: Polymethacrylate-type monoliths functionalized with chiral amino phosphonic acid-derived strong cation exchange moieties for enantioselective nonaqueous capillary electrochromatography and investigation of the chemical composition of the monolithic polymer
AUTHOR(S): Preinerstorfer, Beatrix; Lindner, Wolfgang; Laemmerhofer, Michael
CORPORATE SOURCE: Christian Doppler Laboratory for Molecular Recognition
Materials, Institute of Analytical Chemistry, University of Vienna, Vienna, Austria
SOURCE: Electrophoresis [illegible] 26(10), 2005-2018
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In situ prepared monolithic poly(glycidyl methacrylate-co-ethylene dimethacrylate) (poly(GMA-co-EDMA)) capillary columns were activated to reactive thiol-monoliths and subsequently functionalized with (S)-N-(4-allyloxy-3,5-dichlorobenzoyl)-2-amino-3,3-dimethylbutanephosphonic acid as chiral selector by radical addition to afford enantioselective strong cation exchanger (SCX) capillary columns (100 μm inner diameter (ID)). These monolithic capillaries were devised for the enantiosepn. of chiral bases by nonaq. and aqueous capillary electrochromatog. (CEC) and the results obtained for mefloquine and its tert-butylcarbamate as test compds. were compared to those obtained with particulate silica-based analogs (packed columns). Despite abolishment of nonspecific ionic interactions between the cationic solutes and residual silanols that may diminish separation factors of the silica-based chiral SCX particles, the poly(GMA-co-EDMA)-supported SCX monolith did not, as expected, show better enantioselectivities, which was assumed to be due to detrimental nonspecific interactions between the analytes and the lipophilic polymer backbone. To minimize these unfavorable contributions, less lipophilic monoliths were developed by copolymn. of different amts. of the hydrophilic monomer 2-hydroxyethyl methacrylate (HEMA) with GMA and EDMA, leading to GMA-co-HEMA-co-EDMA-terpolymeric monoliths. By this increase of the hydrophilicity of the monolithic support the enantioselectivity of the resultant SCX stationary phase could be enhanced and reached values comparable to the packed silica-based enantioselective SCX capillaries. Addnl., the mobile phase composition and other variables were examined and it could be shown that the separation factors are considerably affected by diverse parameters such as acetonitrile-methanol ratio and type and concentration of the counterion. Mefloquine enantiomers could be separated with α-values up to 1.56 and a maximum plate count of .apprx.60,000 m-1 could be achieved.
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 40 CA COPYRIGHT 2007 ACS on STN (Continued)

L16 ANSWER 5 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 141:98694 CA
TITLE: Stereoselectivity in the pharmacodynamics and pharmacokinetics of the chiral antimalarial drugs
AUTHOR(S): Brocks, Dion R.; Mehvar, Reza
CORPORATE SOURCE: Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Can.
SOURCE: Clinical Pharmacokinetics (2003), 42(15), 1359-1382
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Several of the antimalarial drugs are chiral and administered as the racemate. These drugs include chloroquine, hydroxychloroquine, quinacrine, primaquine, mefloquine, halofantrine, lumefantrine and tafenoquine. Quinine and quinidine are also stereoisomers, although they are given sep. rather than in combination. From the perspective of antimalarial activity, most of these agents demonstrate little stereoselectivity in their effects in vitro. Mefloquine, on the other hand, displays in vitro stereoselectivity against some strains of P. falciparum, with a eudismic ratio of almost 2:1 in favor of the (+)-enantiomer. Addnl., for some of these agents (e.g. halofantrine, primaquine, chloroquine), stereoselectivity has been noted in the ability of the enantiomers to cause certain adverse effects. In recent years, stereospecific anal. methods capable of measuring the individual enantiomers after the administration of racemic drugs have been reported for a number of chiral antimalarial drugs. These assays have revealed that almost all the studied antimalarial drugs display stereoselectivity in their pharmacokinetics, leading to enantioselectivity in their plasma concns. Whereas the oral absorption of these agents appears to be non-stereoselective, stereoselectivity is often seen in their volume of distribution and/or clearance. With regard to distribution, plasma protein binding of some chiral antimalarial drugs exhibits a significant degree of stereoselectivity, leading to stereoselective distribution to blood cells and other tissues. Because of their low hepatic extraction ratios, stereoselective plasma protein binding also contributes to the stereoselectivity in the metabolism of these drugs. Chiral metabolites are formed from some parent antimalarial drugs, although stereoselective aspects of the pharmacokinetics of the metabolites are not well understood. It is concluded that knowledge of the stereoselective aspects of these agents may be helpful in better understanding their mechanisms of action and possibly optimizing their clin. safety and/or effectiveness.
REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 5 OF 40 CA COPYRIGHT 2007 ACS on STN (Continued)

L16 ANSWER 6 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 141:94451 CA
TITLE: Novel enantioselective strong cation exchangers based on sulfodipeptide selectors: Evaluation for enantiomer separation of chiral bases by nonaqueous capillary electrochromatography
AUTHOR(S): Hebenstreit, Dieter; Bicker, Wolfgang; Laemmerhofer, Michael; Lindner, Wolfgang
CORPORATE SOURCE: Christian Doppler Laboratory for Molecular Recognition Materials, Institute of Analytical Chemistry, University of Vienna, Vienna, Austria
SOURCE: Electrophoresis (2004), 25(2), 277-289
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Strong cation exchange (SCX)-type chiral stationary phases (CSPs) based on β-amino sulfonic acid-terminated dipeptide derivs. as chiral selectors, immobilized on thiolmodified silica particles (3.5 μm), were synthesized and applied to enantiomer sepns. of chiral bases by nonaq. capillary electrochromatog. (CEC). The effect of structural variations of the sulfodipeptide selectors on the separation factors α was investigated. These studies included variation of the acid-terminal amino sulfonic acid residue, variation of the configurations, i.e., comparison of the diastereomeric (S,S)- and (R,S)-configurations of the sulfodipeptides, and finally comparison of sulfodipeptide selectors with corresponding β-amino sulfonic acid analogs. In general, the capillary columns (100 μm ID) packed with the new SCX-type CSPs showed enantioselectivity for an elaborated set of chiral basic drugs in CEC acting by an enantioselective cation-exchange retention mechanism. N-[N-(4-Allyloxy-3,5-dichlorobenzoyl)-leucyl]-2-amino-3,3-dimethylbutane sulfonic acid, in particular with (R,S)-configuration, turned out to be a more effective SCX-type selector than a more rigid analog based on N-[N-(4-Allyloxy-3,5-dichlorobenzoyl)-leucyl]-2-pyrrolidinemethane sulfonic acid. Both of the former diastereomers were capable to baseline-resolve the enantiomers of ca. 40% of the tested basic chiral solutes including sympathomimetics and β-blockers, while for the latter SCX-type CSPs only 10-20% of the selected solutes afforded resolns. > 1.5.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 7 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 140:399416 CA
TITLE: Cerebral uptake of mefloquine enantiomers with and without the P-gp inhibitor elacridar (GF1210918) in mice
AUTHOR(S): De Lagerie, Sylvie Barraud; Comets, Emmanuelle; Gautrand, Celine; Fernandez, Christine; Auchere, Daniel; Singlas, Eric; Mentre, France; Gimenez, Francois
CORPORATE SOURCE: Departement de Pharmacie Clinique, Faculte de Pharmacie, Chatenay-Malabry, 92296, Fr.
SOURCE: British Journal of Pharmacology (2004), 141(7), 1214-1222
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mefloquine is a chiral neurotoxic antimalarial agent showing stereoselective brain uptake in humans and rats. It is a substrate and an inhibitor of the efflux protein P-glycoprotein. We investigated the stereoselective uptake and efflux of mefloquine in mice, and the consequences of the combination with an efflux protein inhibitor, elacridar (GF120918) on its brain transport. Racemic mefloquine (25 mg kg-1) was administered i.p. with or without elacridar (10 mg kg-1). Six to seven mice were killed at each of 11 time-points between 30 min and 168 h after administration. Blood and brain concns. of mefloquine enantiomers were determined using liquid chromatog. A three-compartment model with zero-order absorption from the injection site was found to best represent the pharmacokinetics of both enantiomers in blood and brain. (-)Mefloquine had a lower blood and brain apparent volume of distribution and a lower efflux clearance from the brain, resulting in a larger brain/blood ratio compared to (+) mefloquine. Elacridar did not modify blood concns. or the elimination rate from blood for either enantiomers. However, cerebral AUCinf of both enantiomers were increased, with a stronger effect on (+) mefloquine. The efflux clearance from the brain decreased for both enantiomers, with a larger decrease for (+)mefloquine. After administration of racemic mefloquine in mice, blood and brain pharmacokinetics are stereoselective, (+)mefloquine being excreted from brain more rapidly than its antipode, showing that mefloquine is a substrate of efflux proteins and that mefloquine enantiomers undergo efflux in a stereoselective manner. Moreover, pretreatment with elacridar reduced the brain efflux clearances with a more pronounced effect on (+)mefloquine.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 8 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 140:117538 CA
TITLE: Enantioseparation of erythro-mefloquine and its analogues in capillary electrophoresis
AUTHOR(S): Chankvetadze, Bezhan; Burjanadze, Naira; Blaschke, Gottfried
CORPORATE SOURCE: School of Chemistry, Molecular Recognition and Separation Science Laboratory, Tbilisi State University, Tbilisi, GA, 380028, USA
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (2003), 32(1), 41-49
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The enantioseps. of the chiral antimalaria drug (R,S)-erythro-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (erythro-mefloquine, erythro-MQ) and its analogs were studied by capillary electrophoresis (CE) using cyclodextrins (CDs) as chiral selectors. The emphasis was put on the enantiomer affinity pattern of MQ towards different CDs as well as on simultaneous enantioseps. of erythro-MQ and its structural analogs. All 3 native CDs resolved the enantiomers of erythro-MQ and the enantiomer affinity pattern was the same, i.e. (+)-erythro-MQ was the more tightly bond enantiomer. However, the affinity pattern of erythro-MQ enantiomers was opposite in the case of heptakis-(2,3,6-tri-O-methyl)-β-CD (TM-β-CD), heptakis-(2,3-di-O-methyl-6-sulfo)-β-CD (HDMS-β-CD), heptakis-(3-O-methyl-2,6-di-O-sulfo)-β-CD (HMdiSu-β-CD) and randomly sulfated β-CD (SU-β-CD). Randomly hydroxyalkylated and acetylated derivs. of CDs appeared to be suitable chiral selectors for simultaneous enantiosepn. of erythro-MQ and its analogs.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 9 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:202672 CA
TITLE: Comparative enantioseparations with native β-cyclodextrin, randomly acetylated β-cyclodextrin and heptakis-(2,3-di-O-acetyl)-β-cyclodextrin in capillary electrophoresis
AUTHOR(S): Chankvetadze, Bezhan; Lomsadze, Ketevan; Burjanadze, Naira; Breitkreutz, Joerg; Pintore, Giorgio; Chessa, Mario; Bergander, Klaus; Blaschke, Gottfried
CORPORATE SOURCE: Molecular Recognition and Separation Science Laboratory, School of Chemistry, Tbilisi State University, Tbilisi, Gabon
SOURCE: Electrophoresis (2003), 24(6), 1083-1091
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Comparative enantioseps. were performed with three neutral cyclodextrins (CDs) in capillary electrophoresis (CE). In particular, native β-CD was compared with single component heptakis(2,3-di-O-acetyl)-β-CD (HDA-β-CD) and randomly acetylated β-CD (Ac-β-CD) with the emphasis on the enantiomer migration order. The opposite affinity of the enantiomers of several chiral analytes was observed towards native β-CD and its acetylated deriva. The enantiomer affinity pattern of some chiral analytes was also opposite towards the two acetylated deriv. of β-CD. In the case of the chiral drug clenbuterol (CL) an attempt was made to evaluate the possible structural reasons of the affinity reversal using one- and two-dimensional as well as transverse rotating frame nuclear Overhauser effect spectroscopy (ROESY). Significant differences were observed between the structure of the CL complexes with β-CD and HDA-β-CD.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 10 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:106588 CA
TITLE: Strong versus weak chiral cation exchangers: comparative evaluation for enantiomer separation of chiral bases by non-aqueous CEC
AUTHOR(S): Zarbl, Elfriede; Lammerhofer, Michael; Woschek, Anna; Hammerschmidt, Friedrich; Parenti, Carlo; Cannazza, Guiseppe; Lindner, Wolfgang
CORPORATE SOURCE: Christian Doppler Laboratory for Molecular Recognition Materials, Institute of Analytical Chemistry, University of Vienna, Vienna, A-1090, Austria
SOURCE: Journal of Separation Science (2002), 25(15-17), 1269-1283
CODEN: JSSCCJ; ISSN: 1615-9306
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Novel enantioselective silica-supported strong and weak cation exchange (SCX and WCX) materials (3.5 μm particles) based on enantiomerically pure N-(4-allyloxy-3,5-dichlorobenzoyl)-2-amino-3,3-dimethylbutanesulfonic acid and corresponding phosphonic acid as well as carboxylic acid structural analogs as chiral selectors have been evaluated for enantiomer separation of chiral bases by non-aqueous capillary electrochromatog. (CEC). Capillary columns packed with these chiral stationary phases (CSPs) showed enantioselectivity in non-aqueous CEC towards a variety of chiral bases including amino alcs. such as β-sympathomimetics and β-blockers. Chromatog. and electrokinetic properties of the strong and weak chiral cation exchangers were evaluated comparatively in terms of their pH* profile, i.e. in terms of their dependence on the base-to-acid ratio of the background electrolyte. It turned out that the SCX type CSPs, and in particular the one based on the β-amino sulfonic acid show a broader window of applicable and suitable exptl. conditions for CEC. For example, a strong and constant EOF was obtained on the sulfonic acid based CSP over the entire pH* range studied, while the EOF velocity of the carboxylic acid based CSP was slow under acidic conditions. In the separation of chiral bases, the ion-exchange retention mechanism dominated over electrophoretic migration under most conditions, especially on the SCX type CSPs. The SCX phases exhibited reasonable enantioselectivity over a wider pH* range, while the weak chiral cation exchanger (WCX type CSP) showed enantiomer separation capabilities for primary, secondary, and tertiary chiral amines only in the alkaline pH* range. Sulfonic and phosphonic acid based CSPs possess broad spectrum of applicability. For example, clenbuterol enantiomers were well baseline resolved both on sulfonic acid based CSP (α = 1.33, Rs = 14.2) as well as phosphonic acid based CSP (α = 1.13, Rs = 4.9). In contrast, under the same conditions the corresponding carboxylic acid CSP exhibited enantioselectivity α of 1.08 and resolution Rs of 1.3 only.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 10 OF 40 CA COPYRIGHT 2007 ACS on STN (Continued)

L16 ANSWER 11 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 138:65751 CA
TITLE: Comparative enantioseparations with native β-cyclodextrin and heptakis-(2-O-methyl-3,6-di-O-sulfo)-β-cyclodextrin in capillary electrophoresis
AUTHOR(S): Chankvetadze, Bezhan; Burjanadze, Naira; Maynard, Dawn
M.; Bergander, Klaus; Bergenthal, Dieter; Blaschke, Gottfried
CORPORATE SOURCE: Institute of Pharmaceutical and Medicinal Chemistry, University of Munster, Munster, D-48149, Germany
SOURCE: Electrophoresis (2002), 23(17), 3027-3034
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Twenty-three cationic chiral analytes were resolved in capillary electrophoresis using native β-cyclodextrin and single isomer heptakis-(2-O-methyl-3,6-di-O-sulfo)-β-cyclodextrin as chiral selectors. For 12 of 16 chiral analytes resolved with both chiral selectors the enantiomer migration order was opposite. In selected cases the structure of cyclodextrin-analyte complexes in aqueous solution was studied using 1-dimensional transverse rotating frame nuclear
Overhauser and exchange spectroscopy. In contrast to mainly inclusion-type complexes between chiral analytes and β-cyclodextrin, external complexes are formed between the chiral analytes and structurally crowded, highly charged heptakis-(2-O-methyl-3,6-di-O-sulfo)-β-cyclodextrin.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L16 ANSWER 12 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 137:52498 CA
TITLE: Low-molecular-weight chiral cation exchangers: novel chiral stationary phases and their application for enantioseparation of chiral bases by nonaqueous capillary electrochromatography
AUTHOR(S): Tobler, Ernst; Lammerhofer, Michael; Wuggenig, Frank; Hammerschmidt, Friedrich; Lindner, Wolfgang
CORPORATE SOURCE: Institute of Analytical Chemistry, University of Vienna, Vienna, A-1090, Austria
SOURCE: Electrophoresis (2002), 23(3), 462-476
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cation exchange type chiral stationary phases (CSPs) based on 3,5-dichlorobenzoyl amino acid and amino phosphonic acid derivs. as chiral selectors (SOs) and silica as chromatog. support were developed and applied to enantiomer sepns. of chiral bases by nonaq. capillary electrochromatog. (NA-CEC). As a rationale for efficient
CSP development we adopted the combined use of the "reciprocity principle of chiral recognition" and nonaq. ion-pair CE as screening assay. Thus, (S)-atenolol was employed as chiral counter-ion added to the BGE in CE and a series of N-derivatized amino acids and amino
phosphonic acids were screened to derive reciprocally information on their
chiral recognition abilities for atenolol enantiomers. Two SO candidates, namely N-(3,5-dichlorobenzoyl)-O-allyl-tyrosine and N-(4-allyloxy-3,5-dichlorobenzoyl)-1-amino-3-methylbutane phosphonic acid that was identified as potential SOs in the CE screening were, after immobilization on thiol-modified silica, evaluated in cation-exchange NA-CEC. The strong chiral cation exchanger with the free phosphonic acid group exhibited enhanced enantioselectivity compared to the weak chiral cation exchanger with the carboxylic acid group. A wide variety of chiral bases could be successfully resolved on the strong chiral cation exchanger with α-values up to 2.2 and efficiencies up to 375000 m-1 including β-blockers and other amino alcs., local anesthetics like etidocaine, antimalarial agents like mefloquine, Troger's base, phenothiazines like promethazine, and antihistaminics. The influence of several exptl. parameters (electrolyte concentration, acid-base ratio and acetonitrile-methanol ratio) was evaluated.
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L16 ANSWER 13 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:391111 CA
TITLE: Preparative resolution of drug racemates to study the chiroptical properties of their enantiomers
AUTHOR(S): Thunberg, Linda; Andersson, Shalini; Allenmark, Stig; Vessman, Jorgen
CORPORATE SOURCE: Department of Chemistry, Goteborg University, Goteborg, SE-412-96, Swed.
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (2001), Volume Date 2002, 27(3-4), 431-439
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present work is focused on the resolution of ten racemates, in order to
study their chiroptical properties and to test the validity of the requirement specified in the European Pharmacopeia (EP) for demonstrating that a drug entity is a racemate. This work shows that the optical purity
of enantiomers and non racemic mixts. of a number of compds. can be determined
more accurately by circular dichroic (CD) spectroscopy than by a measurement of the angle of rotation (AoR), the EP requirement. Using only the AoR, some of the racemates could not be distinguished from the enantiomers. CD spectroscopy or chiral chromatog. should, therefore, be the technique of choice in the determination of optical purity of a
chiral compound, especially for those exhibiting low AoR.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L16 ANSWER 14 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:290091 CA
TITLE: Role of chiral chromatography in therapeutic drug monitoring and in clinical and forensic toxicology
AUTHOR(S): Williams, Marion L.; Wainer, Irving W.
CORPORATE SOURCE: Department of Oncology, Leicester University, Leicester, UK
SOURCE: Therapeutic Drug Monitoring (2002), 24(2), 290-296
CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Advances in chiral chromatog. sepns. have given pharmacologists and toxicologists the tools to examine unexpected clin. results involving chiral drugs. The ability to unravel complex phenomena associated with drug transport and drug metabolism is presented in this manuscript. The relation between the chirality of the drug mefloquine and the intracellular concns. of the drug cyclosporine is illustrated by examining the effect of the enantiomers of mefloquine on the transport activity of P-glycoprotein (Pgp). These studies were conducted using a liquid chromatog. column containing immobilized Pgp. The results demonstrated that (+)-mefloquine competitively displaced the Pgp substrate cyclosporine whereas (-)-mefloquine had no effect on cyclosporine-Pgp binding. The data suggest that cyclosporine cellular and CNS concns. can be increased through the concomitant administration of (+)-mefloquine. The use of chirality in clin. and forensic situations is also illustrated by the metabolism of the enantiomers of ketamine (KET). The plasma concns. of (+)-KET and (-)-KET and the norketamine metabolites (+)-NK and (-)-NK were measured in rat plasma using enantioselective gas chromatog. The sepns. were accomplished using a gas chromatog. chiral stationary phase based on β-cyclodextrin. The pharmacokinetic profiles of (+)-, (-)-KET and (+)-, (-)-NK were determined in control and protein-calorie malnourished (PCM) rats to determine the effect of PCM on ketamine metabolism and clearance. The results indicate that PCM produced a significant and stereoselective decrease in KET and NK metabolism The data suggest that the effects of environmental factors (smoking, alc. use, diet) and drug interactions (coadministered agents) can be measured using the changes in stereochem. metabolic and pharmacokinetic patterns of KET and similar drugs.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 15 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:31066 CA
TITLE: Development of stereoselective nonaqueous capillary electrophoresis system for the resolution of cationic and amphoteric analytes
AUTHOR(S): Zarbl, Elfriede; Lammerhofer, Michael; Franco, Pilar; Petracs, Marietta; Lindner, Wolfgang
CORPORATE SOURCE: Institute of Analytical Chemistry, University of Vienna, Vienna, A-1090, Austria
SOURCE: Electrophoresis (2001), 22(15), 3297-3307
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A stereoselective ion-pair nonaq. capillary electrophoresis (NACE) method employing the partial filling technique with N-derivatized amino acids, e.g., (R)- and (S)-3,5-dinitrobenzoyl-leucine (DNB-Leu), as chiral selector for the separation of pseudoenantiomeric cinchona alkaloid derivs. and other structurally related basic compds. like the enantiomers of mefloquine is presented. Originating from NACE with cinchona alkaloid derivs. as chiral counterions, this method was developed by application of the reciprocity principle of chiral recognition, which was proven to be valid for stereoselective ion-pair capillary electrophoresis (CE). A variety of basic and amphoteric selectands (SAs) could be well resolved. Thereby, the separation was primarily based on stereoselective ion-pair formation of corresponding SA stereoisomers and mobility differences of free and complexed (ion-paired) SAs. Addnl., in the case of diastereomeric SAs, naturally existing mobility differences between the diastereomers played also a role, but was shown by control expts. with racemic DNB-Leu and without selector (SO) to be of minor contribution to overall separation selectivity. Due to its simplicity, speed, and good reproducibility, the established method can be used for fast screening of cationic as well as amphoteric chiral compds., and therefore is a valuable tool in the development of new chiral selectors and chiral stationary phases. Small sample amts. of the SO (4-5 mg) and only anal. amts. of SAs are needed, and apprx.20-50 compds. per day can be tested.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 16 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 133:183136 CA
TITLE: Separation of enantiomers of drugs by capillary electrophoresis with permethyl-gamma-cyclodextrin as chiral solvating agent
AUTHOR(S): Koppenhoefer, Bernhard; Jakob, Andreas; Zhu, Xiaofeng; Lin, Bingcheng
CORPORATE SOURCE: Institute of Organic Chemistry, University of Tubingen, Germany
SOURCE: Journal of High Resolution Chromatography (2000), 23(6), 413-429
CODEN: JHRCE7; ISSN: 0935-6304
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB High-throughput screening is a promising new approach in anal. chemical Within the framework of an extended screening program (The German-Chinese Drug Screening Program), the enantiosepn. of 86 drugs was investigated by capillary zone electrophoresis in the presence of the chiral solvating agent (CSA) octakis-(2,3,6-tri-O-methyl)-γ-cyclodextrin (TM-γ-CD). By this means, 15 drugs could be separated into enantiomeric pairs. Approx. measures for the degree of interaction (migration retardation factor, Rm) and for the degree of enantiomer recognition (migration separation factors, αm) revealed intriguing patterns that were compared with those found for native γ-cyclodextrin (γ-CD). Although there is a distinct influence of the analyte structure on the electrophoretic data, interpretation remains difficult. Most remarkably, permethylation of γ-CD leads neither to a higher affinity nor to better chiral recognition, in contrast to the findings with α-CD.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 17 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 133:37482 CA
TITLE: Reagent kit for capillary electrophoretic analysis of chiral compounds
INVENTOR(S): Lin, Bingcheng; Zhu, Xiaofeng
PATENT ASSIGNEE(S): Dalian Inst. of Chemical Physics, Chinese Academy of Sciences, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 99 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1218904	A	19990609	CN 1997-119484	19971129
CN 1100261	B	20030129		
PRIORITY APPLN. INFO.:			CN 1997-119484	19971129

AB The title reagent kit contains four chiral selective agents (Φa-cyclodextrin, hydropropyl-Φb-cyclodextrin, dimethyl-Φb-cyclodextrin, and trimethyl-Φb-cyclodextrin), two buffer solution [0.05-0.1M NaH2PO4 buffer solution (pH 2.5), and 0.05-0.1M Na3BO3 buffer solution (pH 8.5)], pH regulator (0.05-0.1M Na2PO4, pH 4.5-5.5), additive (hydropropylcellulose HPMC-100), and two 50 Φmm x 30 cm polyacrylamide-coated quartz capillary columns. NaH2PO4 buffer solution is used for preparation of 0.1 mg/mL alkaline chiral orgs., and Na3BO3 buffer solution for 0.1 mg/mL acid chiral orgs. The work concentration of chiral selective agent is 15-45M. Dimethindene, chlorphenamine, tetryzoline, homatropine, theodrenaline, metaclazepam, mefloquine, warfarin, isothipendyl, ibuprofen, and ketoprofen were successfully resolved by using the reagent kit.

L16 ANSWER 18 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:277050 CA
TITLE: Separation of drugs by capillary electrophoresis. Part
10. Permethyl-alpha-cyclodextrin as chiral solvating agent
AUTHOR(S): Zhu, Xiao Feng; Lin, Bing Cheng; Jakob, Andreas; Wuerthner, Stefan; Koppenhoefer, Bernhard
CORPORATE SOURCE: Dalian Inst. Chemical Phys., Dalian, Peop. Rep. China
SOURCE: Electrophoresis (1999), 20(9), 1878-1889
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Following the German-Chinese Drug Screening Program, 86 racemic drugs were
investigated in capillary zone electrophoresis in the presence of the chiral solvating agent (CSA) hexakis-(2,3,6-tri-O-methyl)-α-cyclodextrin (TM-α-CD). Of the 86 drugs, 23 were separated into enantiomeric pairs. A comparison of the migration separation factors (αm) and the migration retardation factors (Rm) with previously published data for native α-CD revealed that the "upper-rim" hydroxyl groups do not necessarily facilitate the recognition of the drug enantiomers by the chiral host. In contrast, an overall increase in affinity for the permethylated host led to a higher rate of successful enantiomer sepns. A key substructure (4H) was identified in the analyte structure domain, with a crucial influence on the behavior of a particular drug.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L16 ANSWER 19 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 130:90128 CA
TITLE: Cerebral uptake of mefloquine enantiomers in fatal cerebral malaria
AUTHOR(S): Pham, Y. T.; Nosten, F.; Farinotti, R.; White, N. J.; Gimenez, F.
CORPORATE SOURCE: Pharmacie Clinique, Faculte Pharmacie, Chatenay-Malabry, Fr.
SOURCE: International Journal of Clinical Pharmacology and Therapeutics (1999), 37(1), 58-61
CODEN: ICTHEK; ISSN: 0946-1965
PUBLISHER: Dustri-Verlag Dr. Karl Feistle
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The brain disposition was studied of the enantiomers of the antimalarial mefloquine in 2 post-mortem cerebral biopsies after oral administration of the racemic mixture using a chiral liquid chromatog. method. Concns. were higher in brain compared to blood plasma.
Studied in 1 patient, white matter concns. were higher compared to gray matter. Based on the ratios brain/plasma, the brain penetration of the (+)enantiomer was much higher.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L16 ANSWER 20 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 129:140784 CA
TITLE: Separation of enantiomers of drugs by capillary electrophoresis. Part 8. β-Cyclodextrin as chiral solvating agent
AUTHOR(S): Lin, B.; Zhu, X.; Wuerthner, S.; Epperlein, U.; Koppenhoefer, B.
CORPORATE SOURCE: Institute of Chemical Physics, Dalian, Peop. Rep. China
SOURCE: Talanta (1998), 46(4), 743-749
CODEN: TLNTA2; ISSN: 0039-9140
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB As part of a comprehensive screening program on the separation of chiral drugs by capillary zone electrophoresis the enantiomeric separation of 54 drug racemates using β-cyclodextrin as a chiral solvating agent was investigated. This study complements previous studies
on 34 drug racemates. Fourteen out of the 54 analytes investigated were separated into the enantiomers, yielding on overall success rate of 24.4% for
a total of 86 drug racemates investigated.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L16 ANSWER 21 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 129:113653 CA
TITLE: Separation of enantiomers of drugs by capillary electrophoresis. Part 6. Hydroxypropyl-β-cyclodextrin as chiral solvating agent
AUTHOR(S): Lin, Bing Cheng; Zhu, Xiao Feng; Epperlein, Ulrich; Schwierskott, Marc; Schlunk, Rainer; Koppenhoefer, Bernhard
CORPORATE SOURCE: Institute Chemical Physics, Dalian, Peop. Rep. China
SOURCE: Journal of High Resolution Chromatography (1998), 21(4), 215-224
CODEN: JHRCE7; ISSN: 0935-6304
PUBLISHER: Huethig GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Following an extended screening project, 86 racemic drugs were investigated by capillary zone electrophoresis in the presence of the chiral solvating agent (CSA) hydroxypropyl-β-cyclodextrin. A total of 42 drugs out of 86 tested was thereby separated into enantiomeric
pairs. Statistical anal. of the numerous expts. performed under identical
conditions reveals a loose correlation of the migration separation factor (αm) with the migration retardation factor (Rm). For a subset of 23 drugs, a drop in the concentration of the CSA was also studied, showing the way
to further optimization.

L16 ANSWER 22 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 128:43736 CA
TITLE: Stereospecific determination of mefloquine in biological fluids by high-performance liquid chromatography
AUTHOR(S): Souri, Effat; Farsam, Hassan; Jamali, Fakhreddin
CORPORATE SOURCE: Department of Medicinal Chemistry, Faculty of Pharmacy, University of Medical Sciences, Tehran, 14155-6451, Iran
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1997), 700(1 + 2), 215-222
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A sensitive stereoselective HPLC method was developed for determination of mefloquine (MFQ) enantiomers in plasma, urine and whole blood. The assay involved liquid-liquid extraction of MFQ from biol. fluids with a mixture of hexane and isopropanol in the presence of sodium hydroxide and derivatization of the residue by (+)-(S)-naphthylethylisocyanate (NEIC) as chiral derivatizing reagent. Separation of the resulting diastereomers was performed on a silica normal-phase column using chloroform-hexane-methanol (25:74:1) as the mobile phase with a flow-rate of 1 mL/min. Using 200 μl of plasma or whole blood, the limit of determination was 0.2 μg/mL with UV detection for both enantiomers. The limit of determination in 500 μl of urine was 0.08 μg/mL with UV detection.

L16 ANSWER 23 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 127:126704 CA
TITLE: Separation of enantiomers of drugs by capillary electrophoresis. Part 4: hydroxypropyl-gamma-cyclodextrin as chiral solvating agent
AUTHOR(S): Koppenhoefer, Bernhard; Epperlein, Ulrich; Zhu, Xiaofeng; Lin, Bingcheng
CORPORATE SOURCE: Institute for Organic Chemistry, University of Tubingen, Tubingen, D-72076, Germany
SOURCE: Electrophoresis (1997), 18(6), 924-930
CODEN: ELCTDN; ISSN: 0173-0835
PUBLISHER: Wiley-VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In an extended chiral drug screening program, enantiosepn. of 86 racemic drugs was tested with hydroxypropyl-γ-cyclodextrin as chiral solvating agent (CSA). A total of 30 drugs out of 86 could be resolved in this straightforward approach. The number of expts. performed under identical conditions allows a statistical treatment of the data. The enantiosepn. of the analytes is correlated with their interaction strength with the CSA. Hence, the concentration of the CSA is a crucial parameter for optimization of the enantiosepn., as shown by a subset of 23 examples.

L16 ANSWER 24 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 126:94891 CA
TITLE: Investigation of 123 chiral drugs by cyclodextrin-modified capillary electrophoresis
AUTHOR(S): Lin, Bingcheng; Zhu, Xiaofeng; Koppenhoefer, Bernhard; Epperlein, Ulrich
CORPORATE SOURCE: Dalian Institute Chem. Phys., Chinese Academy Sciences, Dalian, 116012, Peop. Rep. China
SOURCE: LC-GC (1997), 15(1), 40, 44-46
CODEN: LCGCE7; ISSN: 0888-9090
PUBLISHER: Advanstar
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated 123 drugs for chiral separation using seven cyclodextrins as chiral solvating additives for capillary zone electrophoresis. Of 86 detectable marketed chiral drugs, they separated 63 into enantiomers, including all 23 drugs with tricyclic (aromatic ring number) systems and 9 β-blocker drugs. Native β-cyclodextrin and its derivs. were promising chiral selectors compared with other cyclodextrins because of the mol.'s higher degree of asymmetry.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 25 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 125:309224 CA
TITLE: Chiral separation of basic drugs in cyclodextrin modified capillary zone electrophoresis
AUTHOR(S): Ji, Yibing; Chen, Yuying; Lin, Bingcheng
CORPORATE SOURCE: Department of Analytical Chemistry, China Pharmaceutical University, Nanjing, 210038, Peop. Rep. China
SOURCE: Zhongguo Yaoke Daxue Xuebao (1996), 27(4), 230-234
CODEN: ZHYXE9; ISSN: 1000-5048
PUBLISHER: Zhongguo Yaoke Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB A cyclodextrin-modified electrophoresis system was used to sep. enantiomeric drugs, orciprenaline, isoprenaline, propranolol, nadolol, homatropine, and mefloquine. An acidic buffer (pH 2.5) with cyclodextrin (CD) was used. The basic reason of chiral recognition was the difference in the complexation of both enantiomers, resulting from the difference in hydrophobic affinity and in hydrogen-bonding between the analyte and cyclodextrin. The important effects of variation of β-CD concentration, organic additives, electroosmotic flow (EOF) were recognized.

L16 ANSWER 26 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 125:257330 CA
TITLE: Use of cyclodextrins in the capillary electrophoretic separation of erythro- and threo-mefloquine enantiomers
AUTHOR(S): Fanali, Salvatore; Camera, Emanuela
CORPORATE SOURCE: Istituto di Cromatografia del C.N.R., Area della Ricerca di Roma, P.O. Box 10, 00016 Monterotondo Scalo, Rome, Italy
SOURCE: Journal of Chromatography, A (1996), 745(1+2), 17-23
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Capillary zone electrophoresis was used for the enantiomer separation of mefloquine diastereoisomers and enantiomers using a background electrolyte at acidic pH supplemented with β-cyclodextrin derive. as chiral selectors. The cyclodextrin type and concentration strongly influenced the chiral resolution and among the cyclodextrins used (β-cyclodextrin, dimethylated-, trimethylated- and carboxymethylated-β-cyclodextrin), 2,6,-di-O-methyl-β-cyclodextrin permitted a very good resolution for all the optical isomers even at very low concns. The optimized electrophoretic method resulted to be very reproducible for both migration time and peak areas with a good detection limit (1·10-6 M gave a signal to noise ratio = 3 for each enantiomer). The anal. of a pharmaceutical preparation did not reveal the presence of the threo isomers but only the racemic erythro-mefloquine. Method recovery values, performed on a pharmaceutical preparation, were found in the range 99-102%.

L16 ANSWER 27 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 125:75290 CA
TITLE: Stereoselective pharmacokinetics of mefloquine in young children
AUTHOR(S): Bourahla, A.; Martin, C.; Gimenez, F.; Singhasivanon, V.; Attanath, P.; Sabchearon, A.; Chongsuphajaisiddhi, T.; Farinotti, R.
CORPORATE SOURCE: Hopital Pitie Salpetriere Service, Paris, F-75651/13, Fr.
SOURCE: European Journal of Clinical Pharmacology (1996), 50(3), 241-244
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The stereospecificity of mefloquine pharmacokinetics in children has been investigated. Twelve children aged 6 to 24 mo were treated for uncomplicated falciparum malaria with a single oral dose of 25 mg·kg-1 racemic mefloquine in combination with sulfadoxine and pyrimethamine. Concns. of mefloquine enantiomers were determined using a coupled achiral-chiral chromatog. system. Pharmacokinetic parameters were calculated using model-independent anal. Maximum plasma concns., areas under the curve and apparent plasma elimination half-lives were higher for the (-) enantiomer than its antipode. In contrast, the apparent volume of distribution (V/f) and total clearance (Cl/f) values were higher for the (+) enantiomer. The stereoselectivity of mefloquine pharmacokinetics is similar to that observed in adults.

L16 ANSWER 28 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 124:37837 CA
TITLE: Separation of enantiomers of drugs by capillary electrophoresis. I. γ-Cyclodextrin as chiral solvating agent
AUTHOR(S): Koppenhoefer, B.; Epperlein, U.; Christian, B.; Ji, Yibing; Chen, Yuying; Lin, Bingcheng
CORPORATE SOURCE: Institute of Organic Chemistry, Eberhard-Karls-University Tuebingen, Auf der Morgenstelle 18, Tubingen, D-72076, Germany
SOURCE: Journal of Chromatography, A (1995), 717(1 + 2), 181-90
CODEN: JCRAEY; ISSN: 0021-9673
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Enantiomer separation was studied for a set of 57 chiral drugs. Seven enantiomeric pairs could be separated without recourse to an optimization procedure when using γ-cyclodextrin as chiral solvating agent in capillary zone electrophoresis. Possible interaction mechanisms between selector and selectand mols. are briefly discussed.

L16 ANSWER 29 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 124:37821 CA
TITLE: A comparison of LC and SFC for cellulose- and amylose-derived chiral stationary phases
AUTHOR(S): Bargmann-Leyder, Nathalie; Tambute, Andre; Caude, Marcel
CORPORATE SOURCE: Lab. Chim. Analytique, Ecole Superieure de Physique et Chimie Industrielles de Paris, Paris, Fr.
SOURCE: Chirality (1995), 7(5), 311-25
CODEN: CHRLEP; ISSN: 0899-0042
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study presents a systematic comparison of liquid chromatog. (LC) and supercrit. fluid chromatog. (SFC) for Chiralcel OD and Chiralpak AD chiral stationary phases (CSPs), performed using various chiral compds. having a known or potential pharmaceutical activity. The chiral recognition mechanisms involved in LC and SFC for the enantiomeric separation of β-blockers were studied. It appears that the presence of polar functions, like primary or secondary hydroxyl or amine functions, may result in marked discrepancies in selectivity between LC and SFC. This result is peculiar to cellulose-and amylose-derived CSPs, for which the interactions involved in chiral recognition mechanism are not always well balanced, contrary to what happens for independent CSPs. In the case of chiral resolution of polar solutes or polymer-type CSPs, the analyst should try both the LC and SFC techniques to be able to choose the more stereoselective one.

L16 ANSWER 30 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 121:92009 CA
TITLE: About some aspects of the use of charged cyclodextrins for capillary electrophoresis enantio-separation
AUTHOR(S): Chankvetadze, Bezhan; Endresz, Gabriele; Blaschke, Gottfried
CORPORATE SOURCE: Dep. Pharm. Chem., Univ. Muenster, Muenster, Germany
SOURCE: Electrophoresis (1994), 15(6), 804-7
CODEN: ELCTDN; ISSN: 0173-0835
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Free capillary zone electrophoresis with the neg. charged polyanion of the β-cyclodextrin sulfobutyl ester (SBE-β-CD) as a chiral additive was used for the resolution of basic racemic drugs. High enantioselectively was established for some racemic compds. using extremely low (micromolar) concns. of the chiral additive. The dependencies of the migration times and the selectivity of the enantio-separation on the concentration of the chiral additive and the pH of the run buffer were studied. Examples of the chiral separation in counter-current flows of discrete zones of the chiral selector and the racemic compound as well as separation of the neutral racemic compound thalidomide in a micellar electrokinetic chromatog.-like mode were demonstrated using SBE-β-CD.

L16 ANSWER 31 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 120:289336 CA
TITLE: Stereoselective Pharmacokinetics of Mefloquine in Healthy Caucasians after Multiple Doses
AUTHOR(S): Gimenez, Francois; Pennie, Ross A.; Koren, Gideon; Wainer, Irving W.; Farinotti, Robert; Crevoisier, Charles
CORPORATE SOURCE: Hopital Pitie Salpetriere, Paris, Fr.
SOURCE: Journal of Pharmaceutical Sciences (1994), 83(6), 824-7
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mefloquine (MQ) is a chiral antimalarial agent effective against chloroquine-resistant Plasmodium falciparum. It is com. available as a racemic mixture of the (+) and (-) enantiomers for oral administration. The pharmacokinetics of the (+) and (-) enantiomers of MQ were studied in eight healthy volunteers after administration of a first oral dose of 250 mg of racemic MQ and at steady state after 13 repeated doses of 250 mg given at 1-wk intervals. Plasma samples were collected, and concns. of each enantiomer were determined using a previously described achiral-chiral double column-switching liquid chromatog. method. At each time point, higher plasma concns. values were found for the (-) enantiomer ($p < 0.001$). At steady state, Cmax values of (-)-MQ were higher than those of (+)-MQ (1.42 ± 0.19 vs. 0.26 ± 0.05 mg/L; $p < 0.001$). Similarly, the plasma concns. 7 days after the final dose were higher for (-)-MQ (1.01 ± 0.26 vs. 0.11 ± 0.04 mg/L; $p < 0.001$). AUC values at steady state were also higher for (-)-MQ (197.3 ± 36.7 vs. 30.1 ± 8.9 mg/L·h; $p < 0.001$). The terminal half-life values (T1/2β) were longer for (-)-MQ (430.4 ± 225.2 vs. 172.8 ± 56.5 h; $p < 0.001$). This study shows that the pharmacokinetics of MQ is highly stereoselective.

L16 ANSWER 32 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 120:289265 CA
TITLE: Enantioselective high-performance liquid chromatographic determination of (SR)- and (RS)-mefloquine in plasma using N-benzyloxycarbonylglycyl-L-proline as chiral counterion
AUTHOR(S): Bergqvist, Yngve; Al Kabbani, Jelena; Pettersson, Curt; Huynh Ngoc Hang
CORPORATE SOURCE: Dep. Clin. Chem., Falun Cent. Hosp., Falun, S-791 82, Swed.
SOURCE: Journal of Chromatography, Biomedical Applications (1993), 620(2), 217-24
CODEN: JCBADL; ISSN: 0378-4347
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A stereoselective HPLC method is described for the determination of (SR)- and (RS)-mefloquine in plasma. The direct chiral separation is carried out on a Hypercarb-S column (porous graphitized carbon) with N-benzyloxycarbonylglycyl-L-proline (L-ZGP) as a chiral counterion in a reversed-phase system. The sample work-up included protein precipitation by addition of ZnSO4 and MeCN, followed by liquid-liquid extraction with Me tert-Bu ether. After evaporation of the organic phase, the residue is dissolved in the mobile phase [MeCN-MeOH-acetate buffer (pH 4.6) (48:20:32) plus 5.0 mM L-ZGP] and injected onto the column. Anal. of the enantiomers in plasma after a single oral dose of mefloquine indicated that the pharmacokinetics of the 2 enantiomers are different. The method was validated by determining the absolute recovery, linearity, accuracy, precision and inter- and intraassay variations. The limit of determination was 0.5 μM for the sep. enantiomers.

L16 ANSWER 33 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 120:235256 CA
TITLE: High-performance liquid chromatographic determination of (SR)- and (RS)-enantiomers of mefloquine in plasma and capillary blood sampled on paper after derivatization with (-)-1-(9-fluorenyl)ethyl chloroformate
AUTHOR(S): Bergqvist, Yngve; Doverskog, Magnus; Al Kabbani, Jelena
CORPORATE SOURCE: Dep. Clin. Chem., Falun Cent. Hosp., Falun, S-79182, Swed.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1994), 652(1), 73-81
CODEN: JCBBEP; ISSN: 1387-2273
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A sensitive, stereoselective and rapid reversed-phase liquid chromatog. method for the determination of (SR)- and (RS)-mefloquine enantiomers in 100 μL plasma and capillary blood collected on chromatog. paper is presented. The assay involves protein precipitation from plasma, liquid-liquid extraction of mefloquine from plasma, capillary blood with Me tert.-Bu ether under alkaline conditions and derivatization of MQ with (-)-1-(9-fluorenyl)ethyl chloroformate. Liquid chromatog. separation of the diastereomers was performed using an C18 reversed-phase column with acetonitrile-water-acetic acid 82:18:0.07 (volume/volume/volume) as the mobile phase, and a flow-rate of 1.0 mL/min. When using 100 μL of plasma the limit of determination is 250 nmol/L with UV- and 10 nmol/L with fluorescence detection. The present method offers several advantages over those previously reported; very low limit of determination, small sample volume, sampling onto paper and use of an inexpensive standard achiral HPLC column. No racemization during the derivatization procedure or storage of the MQ enantiomers was found.

L16 ANSWER 34 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 120:207658 CA
TITLE: Chiral separation of amines using reversed-phased ion-pair chromatography
AUTHOR(S): Pettersson, Curt; Gioeli, Carlo
CORPORATE SOURCE: Biomed. Cent., Univ. Uppsala, Uppsala, S-75123, Swed.
SOURCE: Chirality (1993), 5(4), 241-5
CODEN: CHRLEP; ISSN: 0899-0042
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The direct separation of enantiomeric amines was carried out using a chiral counterion, (-)-2,3:4,6,-di-O-isopropylidene-2-keto-L-gulonic acid dissolved in polar mobile phases, water-methanol or isopropanol-acetonitrile. High separation factors, α 1.2-1.7, were obtained for several compds. of pharmacol. interest such as metoprolol, oxprenolol, remoxipride, mefloquine and p-OH-ephedrine.

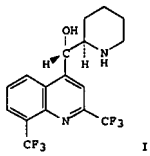
L16 ANSWER 35 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 119:278909 CA
TITLE: Chiral separation of basic drugs using cyclodextrins as chiral pseudo-stationary phases in capillary electrophoresis
AUTHOR(S): Heuermann, M.; Blaschke, G.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Muenster, Hittorfstrasse 58-62, Munster, W-48149, Germany
SOURCE: Journal of Chromatography (1993), 648(1), 267-74
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Capillary electrophoresis was used for the chiral resolution of basic racemic drugs in general and in particular for dimethindene and 4 possible metabolites. Conditions for optimum enantioselectivity and resolution were determined by changing the cyclodextrin type, cyclodextrin concentration, pH of the run buffer, applied current and capillary temperature

L16 ANSWER 36 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 119:278904 CA
TITLE: Chiral resolution of some antimalarial agents by sub- and supercritical fluid chromatography on an (S)-naphthylurea stationary phase
AUTHOR(S): Peytavin, Gilles; Gimenez, Francois; Genissel, Brigitte; Gillotin, Catherine; Baillet, Arlette; Wainer, Irving W.; Farinotti, Robert
CORPORATE SOURCE: Dep. Pharm. Clin., Univ. Paris XI, Paris, Fr.
SOURCE: Chirality (1993), 5(3), 173-80
CODEN: CHRLEP; ISSN: 0899-0042
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The behavior of mefloquine, halofantrine, enpiroline, quinine, quinidine, chloroquine and primaquine is studied by subcrit. fluid chromatog. on a (S)-naphthyl-urea column (250+4.6 mm ID) with a subcrit. mobile phase composed of carbon dioxide, methanol and triethylamine (flow rate of 3 mL/min). Except for primaquine and chloroquine, each enantiomer was separated at a temperature between 40 and 60°, and at a pressure below 15 MPa. A 98/2, volume/volume CO2/methanol 0.1% triethylamine mixture allowed the separation of halofantrine enantiomers while the enantiomers of the more polar metabolite (N-desbutylhalofantrine) were separated with a 80-20 volume/volume mixture as used for mefloquine, enpiroline, quinine and quinidine. The influence of temperature, pressure and of the nature of the mobile phase is discussed.

L16 ANSWER 37 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 119:261916 CA
TITLE: Improved column-switching liquid chromatographic method for the determination of the enantiomers of mefloquine
AUTHOR(S): Gimenez, F.; Dumartin, C.; Wainer, I. W.; Farinotti, R.
CORPORATE SOURCE: Serv. Pharm., Hop. Pitie Salpetriere, Paris, Fr.
SOURCE: Journal of Chromatography, Biomedical Applications (1993), 619(1), 161-6
CODEN: JCBADL; ISSN: 0378-4347
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A liquid chromatog. method for the determination of the enantiomers of mefloquine was improved. The chromatog. involved 2 columns: an achiral cyanopropyl stationary phase for the quantification of (+/-)-mefloquine and a chiral naphthylurea stationary phase for the determination of the enantiomeric ratio. Compared with the previous method, which needed 2 detectors, this one used one detector-integrator to which the 2 columns are connected alternately by an automated column-switching system. The method is suitable for the quantification (0.05 μg/mL) of mefloquine and the determination of enantiomeric ratios from 500-μL plasma samples with UV detection.

L16 ANSWER 38 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 116:242029 CA
TITLE: Enantioselective chromatography of the antimalarial agents chloroquine, mefloquine, and enpiroline on a α1-acid glycoprotein chiral stationary phase: Evidence for a multiple-site chiral recognition mechanism
AUTHOR(S): Aubry, Anne Francoise; Gimenez, Francois; Farinotti, Robert; Wainer, Irving W.
CORPORATE SOURCE: Dep. Oncol., McGill Univ., Montreal, QC, Can.
SOURCE: Chirality (1992), 4(1), 30-5
CODEN: CHRLEP; ISSN: 0899-0042
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of mobile phase pH and dimethyloctylamine (DMOA) on the retention (k') and stereoselectivity (α) of antimalarial agents mefloquine, enpiroline, and chloroquine on the α1-acid glycoprotein chiral stationary phase (AGP-CSP) was investigated. An increase of k' with increasing pH was observed while the effect on α was a function of the solute. The magnitude and direction of changes induced by DMOA depended on pH and the structure of the solute. The results of this study are consistent with a change of the conformation of the AGP between pH 5 and 7. At pH 7, the effect of DMOA on mefloquine was relatively well described by a competitive displacement from one enantioselective site. The effect on chloroquine and enpiroline suggests a multiple-site mechanism in which both competitive and allosteric interactions are involved.

L16 ANSWER 39 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 116:181268 CA
TITLE: A note on direct separation of mefloquine enantiomers by liquid chromatography on a urea-linked chiral stationary phase
AUTHOR(S): Gimenez, F.; Bertrand, F.; Bouley, M.; Thuillier, A.; Hazebroucq, G.; Farinotti, R.
CORPORATE SOURCE: Lab. Pharm. Clin., Univ. Paris XI, Chatenay-Malabry, Fr.
SOURCE: Recent Adv. Chiral Sep., [Proc. Chromatogr. Soc. Int. Symp. Chiral Sep.], 2nd (1990), Meeting Date 1989, 63-6. Editor(s): Stevenson, Derrick; Wilson, Ian D. Plenum: New York, N. Y.
CODEN: 57LHAK
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



I

AB In studies on the separation of the enantiomers of mefloquine (I), a number of stationary phases including (S)-naphthylurea, α-1-glycoprotein, (R)-phenylglycine and polyacrylamide was tested. The (S)-naphthylurea phase was the only one which allowed the separation of the I enantiomers. These results show the influence of modifiers such as methanol or acetonitrile on retention, selectivity and resolution, probably due to a competition of methanol and 2-propanol for the active sites of chiral stationary phase. The lower viscosity of methanol or acetonitrile compared to 2-propanol may also have contributed to these effects.

L16 ANSWER 40 OF 40 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 113:184118 CA
TITLE: Determination of the enantiomers of mefloquine in plasma and whole blood using a coupled achiral-chiral high-performance liquid chromatographic system
AUTHOR(S): Gimenez, Francois; Farinotti, Robert; Thuillier, Alain; Hazebroucq, Georges; Wainer, Irving W.
CORPORATE SOURCE: Pharm. Div., St. Jude Child. Res. Hosp., Memphis, TN, 38105, USA
SOURCE: Journal of Chromatography (1990), 529(2), 339-46
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A coupled achiral-chiral HPLC system has been developed for the determination of the enantiomers of mefloquine, (+)-MFQ and (-)-MFQ, in plasma and whole blood. The MFQ was separated from the interfering components in the biol. matrix and quantified on a cyano-bonded phase, and the enantiomeric composition was determined on an (S)-naphthylurea chiral stationary phase. The two columns were connected by a switching valve equipped with a silica precolumn. The precolumn was used to concentrate the MFQ in the eluent from the achiral column before backflushing onto the chiral phase. The coupled-column system was validated and applied to the anal. of a pilot study of the pharmacokinetics of (+)- and (-)-MFQ in plasma and whole blood.

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=> s l16 not l15
L17          38 L16 NOT L15

=> s l15 not l16
L18           8 L15 NOT L16

=> d ibib abs 1-8
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L18 ANSWER 1 OF 8 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:332558 CA
TITLE: Pharmaceutical composition of (+)-erythro-mefloquine and its use
INVENTOR(S): Baker, Helen Frances; Bannister, Robin Mark
PATENT ASSIGNEE(S): Arakis Ltd., UK
SOURCE: PCT Int. Appl., 8 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005089762	A2	20050929	WO 2005-GB1014	20050317
WO 2005089762	A3	20051103		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2005224154	A1	20050929	AU 2005-224154		20050317
CA 2558096	A1	20050929	CA 2005-2558096		20050317
CN 1929841	A	20070314	CN 2005-80008298		20050317
NO 2006004123	A	20060913	NO 2006-4123		20060913
PRIORITY APPLN. INFO.:			GB 2004-6014	A	20040317
			WO 2005-GB1014	W	20050317

AB A pharmaceutical composition in the form of a unit dosage comprising 1 to 60 mg (+)-erythro-mefloquine, substantially free of the opposite enantiomer, for treatment of an inflammatory condition enantiomer is provided. This is intended for daily dosing. For example, 200 mg tablets of (+)-erythro-mefloquine were prepared containing (A) 4.5 mg, (B) 9 mg, and (C) 18 mg of this agent (4.92 mg, 9.86 mg and 19.71 mg of the HCl salt, resp.), and excipients microcryst. cellulose 76 mg, Povidone 7 mg, Crospovidone 10 mg, sodium lauryl sulfate 2 mg, magnesium stearate 2 mg, and lactose to 200 mg. When tablets were used on a background of methotrexate therapy, adverse effects were observed with the following frequency: placebo 36.8%, A 5.9%, B 22.2%, and C 16.7%. Thus, a combination of (+)-erythro-mefloquine and methotrexate has lower adverse effects than methotrexate alone.

L18 ANSWER 1 OF 8 CA COPYRIGHT 2007 ACS on STN (Continued)

L18 ANSWER 2 OF 8 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:83488 CA
TITLE: Preparation of polymorphic crystalline forms of (+)- and (-)-erythro-mefloquine hydrochloride
INVENTOR(S): Sinden, Kenneth Walter; Baxter, Andrew Douglas; Szelagiewicz, Martin; Hilfiker, Rolf
PATENT ASSIGNEE(S): Arakis Ltd., UK
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005058872	A1	20050630	WO 2004-GB5331	20041217

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2004299340	A1	20050630	AU 2004-299340		20041217
CA 2543076	A1	20050630	CA 2004-2543076		20041217
CN 1882566	A	20061220	CN 2004-80033744		20041217
EP 1753741	A1	20070221	EP 2004-806133		20041217
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR					
NO 2006002137	A	20060911	NO 2006-2137		20060512
PRIORITY APPLN. INFO.:			GB 2003-29236	A	20031217
			WO 2004-GB5331	W	20041217

AB (+)- Or (-)-erythro-Mefloquine hydrochloride can exist in four crystalline forms A, B, C and D, where form A is the most stable form. Form A can be directly produced in morphol. forms like thick columns, cuboids, cubes, and cube-like forms, which can be easily handled during processing and formulation. (+)- Or (-)-erythro-Mefloquine hydrochloride also forms solvates with acetone, 2-butanone, and THF.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 8 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 142:430149 CA
TITLE: Process for the stereospecific synthesis of erythro-mefloquine hydrochloride from a mixture of threo- and erythro-mefloquine via acylation, oxidation, borohydride reduction, and hydrolysis.
INVENTOR(S): Kansal, Vinod Kumar; Maniyan, Padmanilayam Parmeswaran; Deshmukh, Sanjay Shankar; Gupta, Niranjan Lal
PATENT ASSIGNEE(S): Lupin Laboratories Ltd., India
SOURCE: Indian, 19 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 185066	A1	20001104	IN 1998-BO265	19980508
PRIORITY APPLN. INFO.:			IN 1998-BO265	19980508

OTHER SOURCE(S): CASREACT 142:430149
AB A process for stereospecific preparation of (±)-erythro-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol hydrochloride comprises treatment of mefloquine waste, i.e. a mixture of erythro- and threo-mefloquine, with an acylating agent followed by oxidation of the N-acyl product to the ketone and reduction with a metal borohydride and a metallic hydride. Thus, erythro/threo-mefloquine in aqueous NaOH at 0-5° was treated with AcCl followed by stirring for 2 h to give 87% α-(1-acetylpiperidin-2-yl)-2,8-bis(trifluoromethyl)quinolin-4-ylmethanol. The latter was oxidized with Jones reagent in acetone at 0-10° for 1 h to give 91% 1-acetylpiperidin-2-yl 2,8-bis(trifluoromethyl)quinolin-4-yl ketone. This was stirred 1 h with ZnCl2 in DMF; NaBH4 was added followed by stirring for 3 h to give a 90/10 mixture of erythro/threo-N-acetylmefloquine, which was hydrolyzed with HCl in MeOH to give mefloquine hydrochloride (erythro/threo = 90.2:8.2).

L18 ANSWER 4 OF 8 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 142:411244 CA
TITLE: An improved process for the manufacture of erythro-mefloquine hydrochloride
INVENTOR(S): Kansal, Vinod Kumar; Maniyan, Padmanilayam Parmeswaran; Deshmukh, Sanjay Shankar; Gupta, Niranjan Lal
PATENT ASSIGNEE(S): Lupin Laboratories Ltd., India
SOURCE: Indian, 19 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 185394	A1	20010113	IN 1998-BO264	19980508
PRIORITY APPLN. INFO.:			IN 1998-BO264	19980508

OTHER SOURCE(S): CASREACT 142:411244; MARPAT 142:411244
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A process for the stereospecific manufacture of mefloquine hydrochloride [I.HCl; (±)-erythro-α-2-piperidyl-2,8-bis(trifluromethyl)-4-quinolinemethanol hydrochloride] through the intermediacy of α-(1-acyl-α-2-piperidyl) 2,8-bis(trifluoromethyl)quinoline-4-yl ketone [II; R = alkyl, (un)substituted Ph, aralkyl, alkoxy, acyloxy, aralkyloxy] and ketone hydrohalide, i.e. α-2-piperidyl-2,8-bis(trifluromethyl)quinolin-4-yl ketone hydrohalide [III.HX; X = Cl, Br] utilizing a reduction system which would provide the good yield of the erythro mefloquine hydrochloride I.HCl substantially free of the undesired threo diastereoisomer. The process being simple and cost-effective provide for manufacture of the desired biol. active antimalarial compound (no biol. data), the said erythro mefloquine hydrochloride (I), at reduced cost. Thus, acetylating a mixture of racemic erythro and threo mefloquine hydrochloride IV.HCl (yield 87%) followed by oxidation of V [R = Me] with Jones reagent (91%), treatment of a solution of II [R = Me] in MeOH with 6N HCl (51%), and reducing III.HCl with Raney Ni afforded 81% I.

L18 ANSWER 5 OF 8 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:226790 CA
TITLE: Mefloquine for treatment of inflammatory disorders
INVENTOR(S): Skead, Benjamin Mark; Bannister, Robin Mark; Rothaul, Alan
PATENT ASSIGNEE(S): Arakis Ltd., UK
SOURCE: PCT Int. Appl., 5 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002019994	A2	20020314	WO 2001-GB3924	20010831
WO 2002019994	A3	20020516		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2419601	A1	20020314	CA 2001-2419601	20010831
AU 2001084234	A5	20020322	AU 2001-84234	20010831
AU 2001284234	B2	20041104		
EP 1315496	A2	20030604	EP 2001-963202	20010831
EP 1315496	B1	20050817		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001013646	A	20040106	BR 2001-13646	20010831
JP 2004508323	T	20040318	JP 2002-524479	20010831
NZ 524099	A	20040430	NZ 2001-524099	20010831
AT 302008	T	20050915	AT 2001-963202	20010831
PT 1315496	T	20051130	PT 2001-963202	20010831
ES 2245372	T3	20060101	ES 2001-1963202	20010831
ZA 2003001139	A	20040329	ZA 2003-1139	20030211
NO 2003000985	A	20030303	NO 2003-985	20030303
US 2004029916	A1	20040212	US 2003-362784	20030828
US 7034028	B2	20060425		
HK 1054324	A1	20060106	HK 2003-106286	20030903
US 2006074106	A1	20060406	US 2005-290944	20051130
PRIORITY APPLN. INFO.:			GB 2000-21776 A	20000905
			WO 2001-GB3924 W	20010831
			US 2003-362784 A1	20030828

AB A method of treating an inflammatory disease or an autoimmune disease in a subject, comprises the administration of mefloquine. Conditions that may be treated include conditions involving cartilage destruction, inflammatory conditions and those mediated by IL-2 and IL-6, e.g.

L18 ANSWER 5 OF 8 CA COPYRIGHT 2007 ACS on STN (Continued)
rheumatoid arthritis, asthma, psoriasis, psoriatic arthritis, Crohn's disease, irritable bowel syndrome and systemic lupus erythematosus. Other relevant conditions are ulcerative colitis, COPD and asthma. The patient may be disposed to CNS side-effects, and/or may be undergoing concomitant therapy with another drug. The use of (+)-erythro-mefloquine is preferred.

L18 ANSWER 6 OF 8 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 120:289315 CA
TITLE: High-performance liquid chromatographic method for the enantioselective analysis of mefloquine in plasma and urine
AUTHOR(S): Wallen, Leif; Ericsson, Oerjan; Wikstroem, Inger; Hellgren, Urban
CORPORATE SOURCE: Hospital Pharmacy, Southern Hospital, Stockholm, S-118 83, Swed.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1994), 655(1), 153-7
CODEN: JCBBEP; ISSN: 1387-2273
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An HPLC method for anal. of the enantiomers of the antimalarial drug mefloquine is presented. A complete resolution of (-)-(11S,2'R) and (+)-(11R,2'S) erythro-mefloquine from plasma and urine was obtained on a com. AGP column. Mefloquine enantiomers were detected by UV at 222 nm. The separation factor (α) at +20°C was 1.50. The limit of determination (coefficient of variation 4.0%) for the enantiomeric ratio (11S,2'R)/(11R,2'S) is 15:1 at a total mefloquine concentration of 1.6 mM.

L18 ANSWER 7 OF 8 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 120:45206 CA
TITLE: Pharmacological activity and structure-activity relationship of (±)-erythro-mefloquine and related compounds on the isolated mouse phrenic nerve diaphragm preparation
AUTHOR(S): Go, Mei Lin; Lee, How Sung; Ngiam, Tong Lan
CORPORATE SOURCE: Dep. Pharm., Natl. Univ. Singapore, 0511, Singapore
SOURCE: Biological & Pharmaceutical Bulletin (1993), 16(7), 668-74
CODEN: BPBLEO; ISSN: 0918-6158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the antimalarial agent, (±)-erythro-mefloquine and related compds. [(±)-threo-mefloquine, (±)-erythro-N-methylmefloquine and its N-oxide, quinine WR 184806 and halofanthrine] on the isolated mouse phrenic nerve diaphragm preparation were investigated. Based on their pharmacol. effects, these compds. may be divided into two groups. The group I compds., comprising (±)-erythro-mefloquine, (±)-threo-mefloquine and WR 184806, were found to exert a contractile effect on the muscle an also to inhibit the indirectly (nerve) stimulated and directly (muscle) stimulated (after α-bungarotoxin) twitch responses. The group II compds., comprising the other compds. except halofanthrine, lacked a contractile effect on muscle but potentiated the directly stimulated twitch responses (after α-bungarotoxin). Halofanthrine did not elicit any response from the preparation The min. energy conformations of these compds. were determined using an interactive mol. modeling program which incorporates MMX force field for mol. mechanics calcns. Conformational analyses of the erythro and threo isomers of mefloquine hydrochloride were also undertaken using 1H-NMR. THE 1H-NMR data supported the proposal made on the basis of MMX calcns. that the erythro isomer exists in solution as one predominant conformer whereas the threo isomer is present in solution as a mixed population of two stable conformers. The structure-activity relationship of the compds. is discussed.

L18 ANSWER 8 OF 8 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 115:247593 CA
TITLE: Influence of diethylcarbamazine and mefloquine on PGI2 synthesis by the rat thoraic aorta and myometrial tissues
AUTHOR(S): El Tahir, Kamal E. H.; Al-Kharji, Abdulaziz M. H.; Ageel, Abdulrahman M.
CORPORATE SOURCE: Coll. Pharm., King Saud Univ., Riyadh, 11451, Saudi Arabia
SOURCE: General Pharmacology (1991), 22(5), 837-46
CODEN: GEPHDP; ISSN: 0306-3623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of the antifilarial drug diethylcarbamazine citrate (D) and DL-erythro mefloquine hydrochloride (Mf) on PGI2 synthesis by the male rat thoracic aorta and day-20 pregnant rat myometrium was investigated in vitro using a rat platelet antiaggregatory bioassay method. Pretreatment of the tissues with D (25.5-204 μM) or Mf (24-192 μM) for 30 min at 37° significantly inhibited PGI2 synthesis in a concentration-dependent manner. D exhibited its inhibitory effect even in presence of exogenous arachidonic acid (AA) (16.6 μM) whereas Mf lost its inhibitory effect in presence of AA. Pretreatment of urethane-anesthetized rats with D (32 μmol kg-1) but not MF (7.5 μmol kg-1) for 30 min significantly antagonized AA (4 nmol kg-1)-induced hypotension. Furthermore, D (0.25-0.5 μM) antagonized AA-induced aggregation in rabbit platelet-rich plasma without affecting that of ADP. D seemed to interfere with the action of the PG endoperoxide synthase (PG cyclooxygenase) whereas Mf seemed to interfere with the action of phospholipase A2 (PLA2) enzyme. D may have exerted its effect via release of toxic O2 radicals whereas Mf effect may have been due to an interaction with PLA2 substrate phospholipids. The demonstrated inherent property of these two drugs to inhibit the synthesis of the potent vasodilator, platelet antiaggregatory, anticonvulsant and antiinflammatory mediator PGI2 may partly contribute towards better understanding of the biochem. mechanisms that underly some of the previously known but poorly understood actions of these drugs.

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=> s l14 not (l15 or l16)
L19           0 L14 NOT (L15 OR L16)

=> s l11 not (l15 or l16)
L20           3 L11 NOT (L15 OR L16)

=> d ibib abs 1-3
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L20 ANSWER 1 OF 3 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 144:260841 CA
TITLE: Controlled regional oral drug delivery
INVENTOR(S): Jacob, Jules S.; Mathiowitz, Edith; Nangia, Avinash; Shaked, Ze'ev; Moslemy, Peyman
PATENT ASSIGNEE(S): Spherics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 30 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006045865	A1	20060302	US 2005-214206	20050828
WO 2006026504	A2	20060309	WO 2005-US30553	20050829
WO 2006026504	A3	20060810		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
WO 2006039022	A2	20060413	WO 2005-US30552	20050829
WO 2006039022	A3	20060810		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRIORITY APPLN. INFO.:	US 2004-604990P	P	20040827
	US 2004-605198P	P	20040827
	US 2004-605199P	P	20040827
	US 2004-605200P	P	20040827
	US 2004-605201P	P	20040827
	US 2004-607905P	P	20040908

L20 ANSWER 1 OF 3 CA COPYRIGHT 2007 ACS on STN (Continued)

	US 2005-650191P	P	20050204
	US 2005-650375P	P	20050204

AB A composite formulation has been developed for selective, high efficacy delivery to specific regions of the mouth and gastrointestinal tract. The formulation is typically in the form of a tablet or capsule, which may include microparticles or beads. The formulation uses bioadhesive and controlled-release elements to direct release to specific regions, where the drug is absorbed in enhanced amts. relative to the formulation in the absence of the bioadhesive and/or controlled release elements. This is demonstrated by an example showing delivery of gabapentin with a greater area under the curve ("AUC") relative to the FDA reference immediate release drug, i.e., the AUC of the composite bioadhesive formulation is greater than 100% of the AUC of the immediate release drug. In the preferred embodiments, the formulation includes drug to be delivered, controlled release elements, and one or more bioadhesive elements. The bioadhesive polymer may be either dispersed in the matrix of the tablet or applied as a direct compressed coating to the solid oral dosage form. The controlled release elements are selected to determine the site of release. The bioadhesive components are selected to provide retention of the formulation at the desired site of uptake and administration. By selecting for both release and retention at a specific site, typically based on time of transit through the gastrointestinal tract, one obtains enhanced efficacy of uptake of the drug. This is particularly useful for drugs with narrow windows of absorption, and drugs with poor solubility such as the BCE class III and class IV drugs. Bioadhesive gabapentin tables containing gabapentin 56.1, Hypromellose 4000 cps 7.0, Hypromellose 100 cps 28.1, Emcocel 90M 7.0, and magnesium stearate 1.8% in the active core layer; and Spheromer II 90, Povidone K-30 9, and magnesium stearate 1% in the bioadhesive layer. The tablets were administered to dogs and plasma level of gabapentin was measured. The AUC of the tablets exceeded the AUC of immediate-release form.

L20 ANSWER 2 OF 3 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 141:54205 CA
TITLE: Resolution of mefloquine with O,O-di-p-aroyltartaric acids
INVENTOR(S): Baxter, Andrew Douglas; Harris, Michael John; Brown, Stuart
PATENT ASSIGNEE(S): Arakis Ltd., UK
SOURCE: PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004050625	A1	20040617	WO 2003-GB5286	20031204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2503146	A1	20040617	CA 2003-2503146	20031204
AU 2003292382	A1	20040623	AU 2003-292382	20031204
EP 1567500	A1	20050831	EP 2003-767959	20031204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1711246	A	20051221	CN 2003-80103274	20031204
JP 2006514938	T	20060518	JP 2004-556542	20031204
US 2006111573	A1	20060525	US 2005-531128	20050629

PRIORITY APPLN. INFO.:	GB 2002-28430	A	20021205
	GB 2002-29109	A	20021213
	WO 2003-GB5286	W	20031204

AB A process for increasing the optical purity of a mixture of enantiomers of mefloquine, used a single enantiomer of a O,O-di-p-aroyltartaric acid [e.g., O,O-(-)di-p-toluoyl-L-tartaric acid] as a resolving agent, is described.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 3 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 133:213151 CA
TITLE: Pharmaceutical compositions and methods for improved delivery of hydrophobic therapeutic agents
INVENTOR(S): Patel, Manesh V.; Chen, Feng-Jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 13
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050007	A1	20000831	WO 2000-US165	20000105
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6294192	B1	20010925	US 1999-258654	19990226
CA 2365536	A1	20000831	CA 2000-2365536	20000105
AU 2000022242	A	20000914	AU 2000-22242	20000105
AU 771659	B2	20040401		
EP 1158959	A1	20011205	EP 2000-901394	20000105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537317	T	20021105	JP 2000-600619	20000105
NZ 513810	A	20040227	NZ 2000-513810	20000105

PRIORITY APPLN. INFO.:	US 1999-258654	A	19990226
	WO 2000-US165	W	20000105

AB The present invention relates to triglyceride-free pharmaceutical compns. for delivery of hydrophobic therapeutic agents. Compns. of the present invention include a hydrophobic therapeutic agent and a carrier, where the carrier is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon dilution with an aqueous solvent, the composition forms a clear, aqueous dispersion of the surfactants containing the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compns. A pharmaceutical composition contained cyclosporin 0.14, Cremophor RH-40 0.41, Arlacel186 0.29, sodium taurocholate 0.26, and propylene glycol 0.46 mg.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s l10 not (l15 or l16 or l11)
L21           6 L10 NOT (L15 OR L16 OR L11)

=> d ibib abs 1-6
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L21 ANSWER 1 OF 6 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 141:35496 CA
TITLE: Photophysical and photobiological behavior of antimalarial drugs in aqueous solutions
AUTHOR(S): Aloisi, Gian Gaetano; Barbafina, Arianna; Canton, Marcella; Dall'Acqua, Francesco; Elisei, Fausto; Facciolo, Laura; Latterini, Loredana; Viola, Giampietro
CORPORATE SOURCE: Laboratorio di Chimica Fisica, Dipartimento di Chimica, Universita di Perugia, Perugia, 06123, Italy
SOURCE: Photochemistry and Photobiology (2004), 79(3), 248-258
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This article describes the results of a combined photophys. and photobiol. study aimed at understanding the phototoxicity mechanism of the antimalarial drugs quinine (Q), quinacrine (QC) and mefloquine (MQ). Photophys. expts. were carried out in aqueous solns. by stationary and time-resolved fluorimetry and by laser flash photolysis to obtain information on the various decay pathways of the excited states of the drugs and on transient species formed on irradiation The results obtained showed that fluorescence and intersystem crossing account for all the adsorbed quanta for Q and MQ (quantum yield of about 0.1 and 0.9, resp.) and only for 24% in the case of QC, which has a negligible fluorescence quantum yield (0.001). Laser flash photolysis expts. evidenced, for QC and MQ, the occurrence of photoionization processes leading to the formation of the radical cations of the drugs. The effects of tryptophan and histidine on the excited states and transient species of the three drugs were also investigated. In parallel, the photoactivity of the antimalarial drugs was investigated under UV irradiation on various biol. targets through a series of in vitro assays in the presence and in the absence of oxygen. Phototoxicity on 3T3 cultured fibroblasts and lipid photoperoxidn. were observed for all the drugs. The photodamage produced by the drugs was also evaluated on proteins by measuring the photosensitized crosslinking of spectrin. The combined approaches were proven to be useful for understanding the mechanism of phototoxicity induced by the antimalarial drugs.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 6 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 138:66194 CA
TITLE: Adverse effects of the antimalaria drug mefloquine: due to primary liver damage with secondary thyroid involvement?
AUTHOR(S): Croft, Ashley M.; Herxheimer, Andres
CORPORATE SOURCE: Surgeon General's Department, Ministry of Defence, St. Giles' Court, London, WC2H 8LD, UK
SOURCE: BMC Public Health [online computer file] (2002), 2, No pp. given
CODEN: BPHMAJ; ISSN: 1471-2458
URL: http://www.biomedcentral.com/1471-2458/2/6
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB This work critical reviewed 516 published case reports of adverse effects of mefloquine to clarify the phenomenol. of the harms associated with mefloquine and to make recommendations for safer prescribing. It is postulated that many of the adverse effects of mefloquine are a posthepatic syndrome caused by primary liver damage. In some users symptomatic thyroid disturbance apparently occurs, either independently or as a secondary consequence of the hepatocellular injury. The mefloquine syndrome presents in a variety of ways including headache, gastrointestinal disturbances, nervousness, fatigue, disorders of sleep, mood, memory and concentration, and occasionally frank psychosis. Previous liver or thyroid disease, and concurrent insults to the liver (such as from alc., dehydration, an oral contraceptive pill, recreational drugs, and other liver-damaging drugs), may be related to the development of severe or prolonged adverse reactions to mefloquine. People with active liver or thyroid disease probably should not take mefloquine, whereas those with fully resolved neuropsychiatric illness may do so safely. Mefloquine users should avoid alc., recreational drugs, hormonal contraception and comedications known to cause liver damage or thyroid damage. With these caveats, mefloquine may apparently be safely prescribed in pregnancy, and also to occupational groups who carry out safety-critical tasks. Mefloquine's adverse effects need to be investigated through a multicenter cohort study, with small controlled studies testing specific elements of the hypothesis.
REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 6 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 125:48161 CA
TITLE: Current views on the mechanisms of resistance to quinoline-containing drugs in Plasmodium falciparum
AUTHOR(S): Ward, S. A.; Bray, P. G.; Mungthin, M.; Hawley, S. R.
CORPORATE SOURCE: Department Pharmacology and Therapeutics, University Liverpool, Liverpool, L69 3BX, UK
SOURCE: Annals of Tropical Medicine and Parasitology (1995), 89(2), 121-124
CODEN: ATMPA2; ISSN: 0003-4983
PUBLISHER: Saunders
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 12 refs. The issue of chloroquine resistance in Plasmodium falciparum and cross-resistance patterns with other related chemotherapeutic agents has been the subject of intense interest for many years. Despite this level of investigation, the picture remains very unclear. Although it is accepted that chloroquine resistance is, at least in part, a function of reduced drug accumulation, the question of reduced drug uptake vs. enhanced efflux is yet to be resolved at both the mol. and biochem. levels. Further, the absolute cross-resistance patterns of chloroquine-resistant isolates to closely related analogs is a matter for debate, although there appears to be a reciprocal arrangement between resistance to chloroquine and resistance to mefloquine, halofantrine and possibly quinine. Evidence is presented for the coexistence of two or more chloroquine-resistance mechanisms in isolates of P. falciparum, only one of which is verapamil sensitive. In addition, an anal. of cross-resistance patterns, as measured by the inoculum effect, is presented.

L21 ANSWER 4 OF 6 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 125:419 CA
TITLE: Sensitivity of Plasmodium falciparum to reduced dose of mefloquine in pregnant women in Nigeria
AUTHOR(S): Okoyeh, J. N.; Lege-Oguntoye, L.; Emembolu, J. O.; Sarki, U.
CORPORATE SOURCE: Faculty Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria
SOURCE: Acta Tropica (1996), 61(1), 1-8
CODEN: ACTRAQ; ISSN: 0001-706X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mefloquine base, (12.5 mg/kg body weight), was administered as a single oral dose to 34 pregnant women with Plasmodium falciparum parasitemia. They were followed up in vivo using the modified 28-day WHO extended field test. The sensitivity of P. falciparum isolates obtained from these women to mefloquine (MQ) was evaluated in vitro. All women were parasite neg. by day 4 and remained a parasitemic throughout the 28-day period of observation. Parasitol. and clin. responses were well correlated in all the patients. Minimal side effects, after drug intake, were reported by these women, but they all resolved spontaneously. The determined Mean Parasite Clearance Time (MPCT) was 57.7 ± 14 h. Seventeen parasite isolates were cultured in vitro; 9 (53%) grew satisfactorily. Schizont growth inhibitions was obtained at mefloquine concentration of 32 pmol/well (6.4 pmol/μL). The effective drug concentration that gave 99% parasite growth inhibition (EC99) was 25.6 pmol/well (5.1 pmol/μL); which indicates high parasite susceptibility to the drug in vitro. However, low dose of MQ may be ineffective in clearing parasitemia in areas with mefloquine resistant parasite strains.

L21 ANSWER 5 OF 6 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 124:193444 CA
TITLE: Comparison of artemether and quinine in the treatment of severe falciparum malaria in south-east Thailand
AUTHOR(S): Karbwang, J.; Tin, T.; Rimchala, W.; Sukontason, K.; Namsiripongpun, V.; Thanavibul, A.; Na-Bangchang, K.; Laothavorn, P.; Bunnag, D.; Harinasuta, T.
CORPORATE SOURCE: Fac. Tropical Med., Mahidol Univ., Bangkok, Thailand
SOURCE: Transactions of the Royal Society of Tropical Medicine and Hygiene (1995), 89(6), 668-71
CODEN: TRSTAZ; ISSN: 0035-9203
PUBLISHER: Royal Society of Tropical Medicine and Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English
AB One hundred and two Thai patients with severe falciparum malaria (92 males and 10 females) were allocated at random to receive either the standard regimen of quinine infusion (52 cases) or i.m. artemether (50 cases). The patients in both groups had comparable admission clin. and laboratory data. Artemether gave a better survival rate (87.2% vs. 63.3%) and parasite clearance time (54 vs. 78 h) than quinine. Fever clearance times (79 h vs. 84 h) and time to recovery of consciousness (48 h in both groups) were comparable. Previous treatment with quinine or mefloquine had no influence on treatment outcome. The most common adverse effect in patients treated with quinine was tinnitus. Two patients had severe hearing impairment which resolved within 1 wk after the end of treatment. Mild, transient pain was noted at the injection site of artemether but no abscess formed. QTc wave prolongation was seen in most patients receiving quinine; however, no arrhythmia was observed despite the high concentration of quinine in some patients who had received quinine before admission. Complications developed in 7 survivors in each treatment group. No patient in the artemether group had neurol. sequelae after recovery of consciousness, but 2 in the quinine group had left facial palsy and one had a myasthenia gravis-like syndrome. No patient died with complications in the artemether group, but 7 died with pulmonary complications in the quinine group.

L21 ANSWER 6 OF 6 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 118:116178 CA
TITLE: Blood to plasma ratio of mefloquine: interpretation and pharmacokinetic implications
AUTHOR(S): Tajerzadeh, H.; Cutler, D. J.
CORPORATE SOURCE: Coll. Pharm., Tehran Univ., Tehran, Iran
SOURCE: Biopharmaceutics & Drug Disposition (1993), 14(1), 87-91
CODEN: BDDID8; ISSN: 0142-2782
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The blood to plasma ratio of the antimalarial mefloquine has been reported to be close to 1, while other reports indicate extensive accumulation in erythrocytes. This apparent contradiction has been resolved by a quant. examination of the compensating effects of plasma protein binding of mefloquine which almost exactly matches the extent of mefloquine accumulation in erythrocytes. The observed blood to plasma ratio of about 1 arises as the result of a balance between extensive red cell uptake and extensive plasma protein binding. Some pharmacokinetic implications of the distribution of mefloquine within blood are outlined.

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L9 ANSWER 1 OF 3 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 141:54205 CA
TITLE: Resolution of mefloquine with O,O-di-p-aroyltartaric acids
INVENTOR(S): Baxter, Andrew Douglas; Harris, Michael John; Brown, Stuart
PATENT ASSIGNEE(S): Arakis Ltd., UK
SOURCE: PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004050625	A1	20040617	WO 2003-GB5286	20031204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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CN 1711246	A	20051221	CN 2003-80103274	20031204
JP 2006514938	T	20060518	JP 2004-556542	20031204
US 2006111573	A1	20060525	US 2005-531128	20050629

PRIORITY APPLN. INFO.: GB 2002-28430 A 20021205
GB 2002-29109 A 20021213
WO 2003-GB5286 W 20031204

AB A process for increasing the optical purity of a mixture of enantiomers of mefloquine, used a single enantiomer of a O,O-di-p-aroyltartaric acid [e.g., O,O-(-)di-p-toluoyl-L-tartaric acid] as a resolving agent, is described.
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L9 ANSWER 2 OF 3 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:391111 CA
TITLE: Preparative resolution of drug racemates to study the chiroptical properties of their enantiomers
AUTHOR(S): Thunberg, Linda; Andersson, Shalini; Allenmark, Stig; Vessman, Jorgen
CORPORATE SOURCE: Department of Chemistry, Goteborg University, Goteborg, SE-412-96, Swed.
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (2001), Volume Date 2002, 27(3-4), 431-439
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present work is focused on the resolution of ten racemates, in order to study their chiroptical properties and to test the validity of the requirement specified in the European Pharmacopeia (EP) for demonstrating that a drug entity is a racemate. This work shows that the optical purity of enantiomers and non racemic mixts. of a number of compds. can be determined more accurately by circular dichroic (CD) spectroscopy than by a measurement of the angle of rotation (AoR), the EP requirement. Using only the AoR, some of the racemates could not be distinguished from the enantiomers. CD spectroscopy or chiral chromatog. should, therefore, be the technique of choice in the determination of optical purity of a chiral compound, especially for those exhibiting low AoR.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 3 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 119:56308 CA
TITLE: A high-performance liquid chromatographic method for the quantitative enantioselective analysis of mefloquine stereoisomers
AUTHOR(S): Qiu, Yihong; Kitamura, Satoshi; Guillory, J. Keith
CORPORATE SOURCE: Coll. Pharm., Univ. Iowa, Iowa City, IA, 52242, USA
SOURCE: Pharmaceutical Research (1992), 9(12), 1640-3
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A rapid quant., enantioselective HPLC method for the determination of the 4 stereoisomers, (+) and (-) erythro and (+) and (-) threo forms, of mefloquine was developed on a Chiralpak AD anal. column containing amylose tris(3,5-dimethylphenyl carbonate)-coated on silica gel and hexane-EtOH-Et2NH (96:4:0.1) as the mobile phase. This method made it possible to quantitate small amts. of the threo form in the presence of the erythro form of mefloquine, the form which is used as the active ingredient in com. mefloquine tablets. Tablets from 3 sources were studied to determine their optical purity, and it was found that tablets from one source contain 0.27% of the (-)-threo and 0.25% of the (+)-threo form, tablets from the second source contained 0.056 and 0.042% (-)- and (+)-threo, resp., and tablets from the third source contained 0.052% (+)-threo, with the remainder being erythro.

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L5             0 S THREO-MEFLOQUINE/CN
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L8          5110 S OPTICAL PURITY
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L12            3 S L7 AND ?TARTARIC?
L13            0 S THREOMEFLOQUINE
L14            4 S THREO-MEFLOQUINE
L15           10 S ERYTHRO-MEFLOQUINE
L16           40 S L7 AND (CHIRAL OR ACHIRAL)
L17           38 S L16 NOT L15
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Journal of Pharmaceutical and Biomedical Analysis
27 (2002) 431–439

JOURNAL OF
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Preparative resolution of drug racemates to study the chiroptical properties of their enantiomers

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Received 2 July 2001; received in revised form 20 August 2001; accepted 20 August 2001

Dedicated to Professor Dr Gottfried Blaschke on the occasion of his 65th birthday.

Abstract

The present work is focused on the resolution of ten racemates, in order to study their chiroptical properties and to test the validity of the requirement specified in the European Pharmacopeia (EP) for demonstrating that a drug entity is a racemate. This work shows that the optical purity of enantiomers and non racemic mixtures of a number of compounds can be determined more accurately by circular dichroic (CD) spectroscopy than by a measurement of the angle of rotation (AoR), the EP requirement. Using only the AoR, some of the racemates could not be distinguished from the enantiomers. CD spectroscopy or chiral chromatography should, therefore, be the technique of choice in the determination of optical purity of a chiral compound, especially for those exhibiting low AoR.

Keywords: Enantiomer separation; Optical purity; Angle of rotation; CD spectroscopy; Chiroptical properties; European Pharmacopeia

1. Summary

Drugs of today are often marketed as pure enantiomers, whereas drugs of yesterday might exist either as pure enantiomers or as racemates. Racemates of early drugs have seldom been resolved, and consequently, nothing is known about the chiroptical properties of the pure enantiomers. Until recently, there has been a requirement in the European Pharmacopeia (EP) that measurements of the optical rotation should also be carried out for old racemic drugs to demonstrate that a racemate is at hand. However, without knowing the specific rotation of the enantiomer itself or the conditions for its determination, it is difficult to prescribe the correct conditions for measurements of the kind stated.

The present study was focused on the separation of sufficient amounts of pure enantiomers, in order to study the chiroptical properties of the individual enantiomers and to test the validity of the above mentioned requirement. Ten racemates

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0731-7085/02/$ - see front matter
PII: S0731-7085(01)00571-4

in the EP were resolved by chiral chromatography and the specific rotations, as well as the circular dichroic (CD) spectra were measured. Data for the enantiomers, the racemates and for mixtures with one enantiomer in excess were collected. From this work it could be shown that for about half of the compounds studied, a measurement of the angle of rotation (AoR) was not enough to distinguish the enantiomer from the racemate due to low signal to noise ratio. The advantage of using CD is discussed, as with this method it was easy to distinguish a racemate from an enantiomerically enriched sample even in cases when the enantiomeric excess (e.e.) was very small.

The analytical separations and the preparative systems used are discussed and some recommendations given on their suitability.

2. Background

In the last decade, issues on chirality in the pharmaceutical field have moved from being a research topic to production reality. Many companies specialised in commercialisation of chiral drugs have emerged. This development has gone hand in hand with an explosive development of chiral separation media and technologies. However, this situation is as yet not much reflected in the pharmacopoeias, wherein the discrimination between a racemic compound and its pure enantiomers, if available on the market, has by tradition been made by a simple test for optical rotation. Chiral methods are mentioned in the pharmacopoeias, but have to date not been used in many monographs which stipulate the requirements for a pharmaceutical compound. In comparison, optical rotation is a less demanding and also an inexpensive measurement to perform and, therefore, the most commonly used method today.

Until recently, there have been requirements in the EP [1], that even established racemic drugs, of which no pure enantiomers are available on the market, should be treated in the same way, i.e. tested for lack of optical rotation. However, when the pure enantiomers are not available in amounts needed for establishing the optical activity, the conditions required for a measurement are very difficult to predict. The present study, including preparative resolution of some racemic compounds in the EP, was undertaken in order to explore the validity of such a requirement by investigating the chiroptical properties of the enantiomers using polarimetry and CD spectroscopy. The specific rotation and CD spectra were measured for both enantiomers of each drug.

The experimental conditions for the measurement of the optical rotation of the different compounds studied were taken from the requirements in the EP. This means that only water, methanol or dichloromethane were used as solvents. The concentrations used were also as given in the EP, with the analytes in amounts of 10–50 mg/ml. For a compound to be racemic, according to the EP specifications, it should have an AoR less than 0.1° [2]. This value corresponds to a specific rotation of between 2 and 10.

The columns used were selected from the arsenal available in our laboratories, and with which our experience has been favourable in the last few years.

3. Experimental

The compounds that were selected from the EP are listed in Table 1 and their structures given in Fig. 1. The selection was made more or less randomly. All compounds were either obtained from the laboratory of the EP or in-house stock.

4. Chromatography

The separation of the enantiomers was optimised on analytical columns (250 × 4.6 mm I.D.) based on 10 μm silica particles. The chiral stationary phases (CSP) used in this study were Chiralcel OJ [cellulose *tris*-(4-methylbenzoate)] or OD [cellulose *tris*-(3,5-dimethylphenylcarbamate)] and Chiralpak AD [amylose *tris*-(3,5-dimethylphenyl-carbamate)] or AS [amylose *tris*-(1-(S)-phenylethylcarbamate)] [3]. The mobile phase was optimised to give sufficient separation of the enantiomers of the compounds studied and was

based on a hydrocarbon (*iso*-hexane or heptane) with the addition of modifiers such as 1-propanol, 2-propanol, ethanol or acetonitrile. In most cases, a small amount of diethylamine was added to improve the chromatographic performance for these basic analytes. The separations obtained are presented in Table 1.

The analytical separation was transferred to the preparative system after adjustment of the flow rate. The preparative separations were carried out on the same chiral sorbent as in the analytical system using 250 × 20 mm I.D. columns. The different chromatographic conditions used for the resolution of the racemates, and the e.e. obtained, are shown in Table 2. In six cases, the enantiomers were purified by flash chromatography on silica to remove impurities acquired from leakage of chiral material from the column as revealed by CD (see below, purification).

The analytical liquid chromatographic measurements were performed on a system consisting of a Gynkotek HPLC Pump Series P580, a Hewlett Packard series 1100 (loop µl) injector and a Gynkotek UVD340S detector.

The preparative liquid chromatographic system consisted of a Gilson mod. 306 solvent delivery pump, a Gilson mod. 231XL sampling injector (loop 5.8 ml) and a Jasco UV-975 detector. The software used for both systems was Chromeleon© Gynkotek 1997 Version 4.20.

4.1. Polarimetry and CD spectrometry

Measurements of the optical rotations were performed on a Perkin–Elmer 341 LC polarimeter at four wavelengths. In Table 3, only values at 589 nm are given as this is the wavelength for measurement of optical rotation in EP. The solvents used in the measurements of the optical rotations were those stated in EP and the concentration of the isolated enantiomer was usually 10 mg/ml. All measurements were carried out in a 1 dm cell at 20 °C. The enantiomers were studied as free bases.

CD spectra were obtained with a JASCO J-715 spectropolarimeter. The solvents were the same as used for the measurements of the optical rotation. A quartz cell of 1 cm pathlength was used and the temperature was kept at 20 °C.

4.2. Purification

During resolution of some of the racemates by preparative chromatography, leakage of the CSP from the column was observed. Since the chiral selector will also give rise to optical rotation, the enantiomers had to be purified by flash chromatography. The enantiomeric compounds purified were chlorcyclizine, doxapram, mefloquine, metoprolol and promethazine. The columns were packed with silica gel, and for chlorcyclizine and

Table 1
Analytical chiral liquid chromatographic systems for resolution of some racemic pharmaceutical compounds

Compound	Column	Mobile phase	k'_1	k'_2	α
Chlorcyclizine HCl	Chiralpak AD	Heptane/IPA/DEA 99/1/0.1	2.99	4.03	1.35
Doxapram HCl	Chiralcel OJ	IH/1-PrOH/MeOH/DEA 90/8/2/0.1	1.24	3.12	2.52
Fenticonazole nitrate	Chiralpak AS	IH/IPA 80/20	1.76	3.81	1.76
Isoconazole	Chiralcel OJ	IH/IPA/DEA 80/20/0.1	2.14	7.00	3.27
Mefloquine HCl	Chiralpak AD	IH/1-PrOH/DEA 95/5/0.1	0.70	3.38	5.51
Methaqualone	Chiralpak AS	IH/IPA/ACN 99/0.5/0.5	4.36	7.47	1.84
Metixene HCl	Chiralcel OJ	IH/EtOH 80/20	1.25	2.31	1.84
Metoprolol tartrate	Chiralcel OD	IH/IPA/DEA 80/20/0.1	0.32	1.37	4.34
Promethazine HCl	Chiralcel OJ	IH/IPA/DEA 99/1/0.1	2.78	7.13	2.56
Terconazole	Chiralpak AD	IH/IPA/DEA 80/20/0.1	2.66	7.35	2.76

IPA, 2-propanol; DEA, diethylamine; IH, isohexane; 1-PrOH, 1-propanol; ACN, acetonitrile; EtOH, ethanol; MeOH, methanol. The separations were carried out at 25 °C, with a flow rate of 1 ml/min. 50 µl of the test solution, 1 mg/ml was injected.

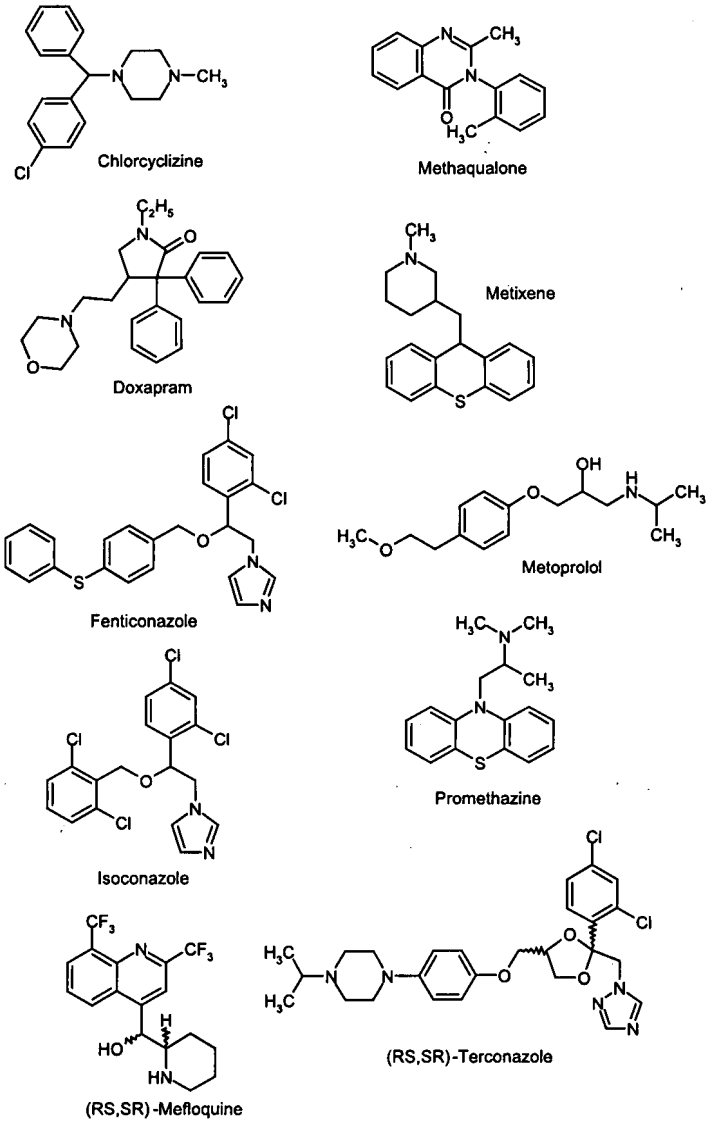

Fig. 1. Structures of the compounds studied.

doxapram, elution was performed with ethyl acetate: dichloromethane:diethylamine (50:50:0.5). Mefloquine and mexitene were eluted with ethyl acetate:2-propanol:diethylamine (50:50:0.5) and metoprolol with ethyl acetate:methanol:diethylamine (25:75:0.5). For promethazine, ethyl acetate:dichloromethane:diethylamine (30:70:0.5) was used.

5. Results and discussion

The analytical separation systems used are presented in Table 1 together with retention data and resolution factors. Four different columns, of which our experience of such separations is good, were used. The preparative separations are documented in Table 2. Some typical chromatograms

are given in Fig. 2, which illustrate the analytical and repetitive preparative resolution of terconazole.

The large α-value of 2.76 makes it possible to resolve 50 mg of the racemate from a single injection. By the repetitive mode shown in Fig. 2, in which the next sample is injected prior to the elution of the second enantiomer, approximately 100 mg of each enantiomer with an e.e. > 96.5% can be isolated in 150 min. In the preparative run, the solvent peak is seen superimposed on the peak from the last eluted enantiomer.

Table 2
Some data from the resolution of 10 racemic compounds by preparative chiral chromatography

Compound	Column	Flow, concentration, amount injected	Amount recovered/mg, E1/E2	e.e., E1/E2
Chlorcyclizine HCl[a]	Chiralpak AD	8 ml/min, 10 mg/ml, 5 mg	37/54	97.5/98.4
Doxapram HCl[a]	Chiralcel OJ	10 ml/min, 20 mg/ml, 6 mg	108/78	97.3/95.3
Fenticonazole nitrate	Chiralpak AS	10 ml/min, 10 mg/ml, 5 mg	67/68	99/97
Isoconazole	Chiralcel OJ	10 ml/min, 25 mg/ml, 37.5 mg	149/155	97.9/99
Mefloquine HCl[a]	Chiralpak AD	10 ml/min, 20 mg/ml, 24 mg	117/107	98.2/97.7
Methaqualone	Chiralpak AS	10 ml/min, 40 mg/ml, 10 mg	116/112	>99/>99
Metixene HCl[a]	Chiralcel OJ	15 ml/min, 24 mg/ml, 29 mg	112/115	99/95
Metoprolol tartrate	Chiralcel OD	10 ml/min, 10 mg/ml, 10 mg	75/82	97.3/98.4
Promethazine HCl[a]	Chiralcel OJ	15 ml/min, 20 mg/ml, 36 mg	93/98	>99/>99
Terconazole	Chiralpak AD	15 ml/min, 10 mg/ml, 50 mg	158/177	99.2/96.5

[a] These compounds were purified by flash chromatography.
For mobile phase composition, see Table 1; e.e., enantiomeric excess.

Table 3
Determination of the optical rotation for some racemic compounds and the corresponding enantiomer

	EP requirements on racemate			First eluted enantiomer concentration 10 mg/ml	
	Angle of rotation (EP requirement)	Solvent	Concentration (mg/ml)	Angle of rotation (measured)	Solvent
Chlorcyclizine HCl				−0.12	MeOH
Doxapram HCl	0.1	Water	50	1.0	Water
Fenticonazole nitrate	0.1	MeOH	10	0.62	MeOH
Isoconazole	0.1	CH_3Cl_2	10	0.3[a]	MeOH
Mefloquine HCl	0.2	MeOH	50	−0.35	MeOH
Methaqualone[b]				1.12	MeOH
Metixene HCl				−0.01	MeOH
Metoprolol					
Tartrate	+7–10	Water	20	0.10	Water
Succinate	0.1	Water			
Prometazine HCl				0.001	MeOH
Terconazole	0.1	CH_3Cl_2	20	0.15	CH_3Cl_2

[a] Concentration, 5 mg/ml.
[b] Atropisomerism.

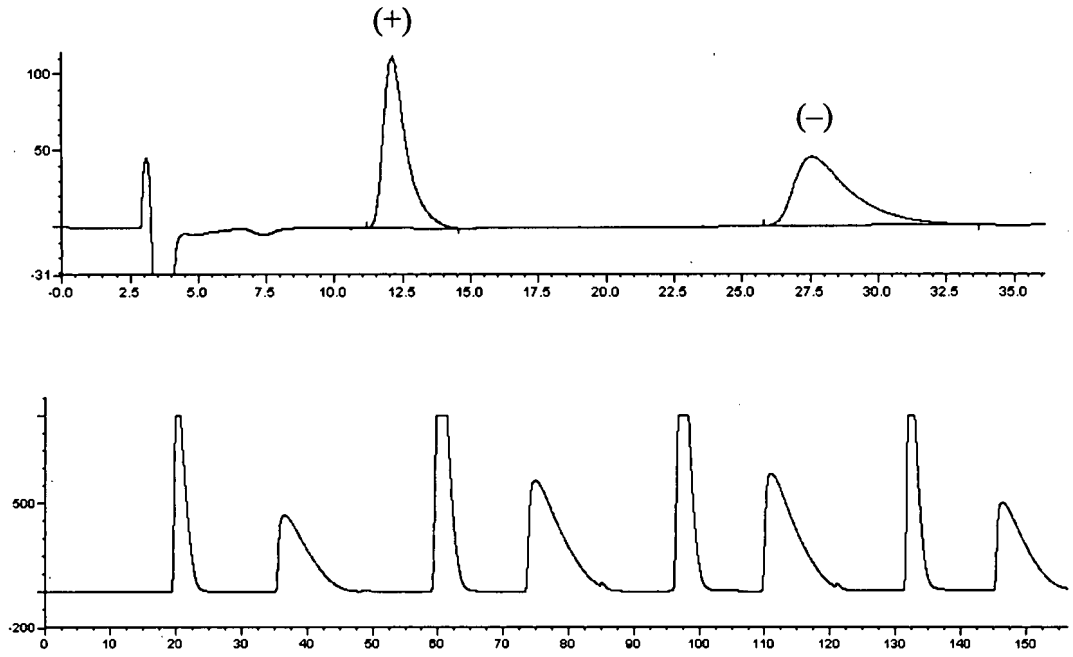

Fig. 2. Analytical and preparative chromatography of terconazole.

The values of the AoR obtained for the first eluted enantiomers are given in Table 3. A general conclusion that can be drawn from this study is that the values are usually quite low. Only in two cases are the values equal to or above 1°. The highest figure was obtained for methaqualone, which exhibits atropisomerism, i.e. there exists no stereogenic centre but a barrier to rotation. There is no requirement in EP 97 for that compound.

Out of the ten substances investigated, four do not have a test for AoR in EP 97. Methaqualone is one of them. The other three are the hydrochlorides of chlorcyclizine, metixene and promethazine, respectively, and they show, indeed, very low values, why it is relevant that there is no test prescribed.

The six substances that have requirements, exhibit AoR for 10 mg/ml that ranges from 0.15° for terconazole to 0.62° for fenticonazole. Isoconazole gave 0.31° for 5 mg/ml and thus, a 10 mg/ml solution would give 0.62°. In Table 4, the AoR is given together with $[\alpha]_D^{20}$ for the five substances showing the lowest AoR. Of these compounds, metixene and promethazine are clearly not differentiated by this test, whereas chlorcyclizine and metoprolol, under the conditions chosen, are at the borderline, i.e. have an AoR slightly higher than 0.10°.

From this presentation, it could be argued that an increase in sample concentration could give rise to a better distinction. However, in many cases that would not suffice, like in the situation for promethazine and metixene.

For two substances, the AoR at different e.e. was measured. The results are given in Table 5. A sample of chlorcyclizine with an e.e. of 40% or even

Table 4
Angle of rotation and specific optical rotation at 589 nm for low responders

Compound	Angle of rotation		$[\alpha]_D^{20}$	
	E1	E2	E1	E2
Chlorcyclizine	−0.120	+0.121	−12.0	+12.1
Metixene	−0.011	+0.013	−1.1	+1.3
Metoprolol	+0.107	−0.097	+10.7	−9.4
Promethazine	+0.001	−0.004	+0.1	−0.4
Terconazole	+0.150	−0.145	+15.0	−14.5

Table 5
Angle of rotation of mixtures with different enantiomeric excess (e.e.)

e.e. %	Angle of rotation	$[\alpha]_D^{20}$
Chlorcyclizine (10 mg/ml in methanol)		
99	−0.120	−12.0
80	−0.092	−9.2
40	−0.048	−4.8
0	−0.001	−0.1
Terconazole (10 mg/ml in dichloromethane)		
96.5	−0.145	−14.5
77	−0.111	−11.1
38	−0.054	−5.4
1.3	+0.003	+0.3

80% would by polarimetry be classified as a racemate with the stipulated requirements. An e.e. of 80% for e.g. (−)-enantiomer, means that there is 90% of this enantiomer and 10% of (+)-chlor-cyclizine. For terconazole, the borderline seems to be around 75% e.e. with an AoR of 0.111° at 77% e.e.

From the results given above, it can be seen that in about half of the measurements undertaken, it would not have been possible to distinguish between the individual enantiomers and the corresponding racemate. Before introducing such a test into a pharmacopoieal monograph, one should first have access to the enantiomers in order to establish conditions for a meaningful measurement.

On the other hand, the CD spectra show a difference between the various mixtures in a very distinct way. The CD measurements are also less demanding with respect to the amount of substance needed. As shown in Fig. 3 for the compounds chlorcyclizine and terconazole, CD absorption bands are readily recognisable even at very low e.e. values.

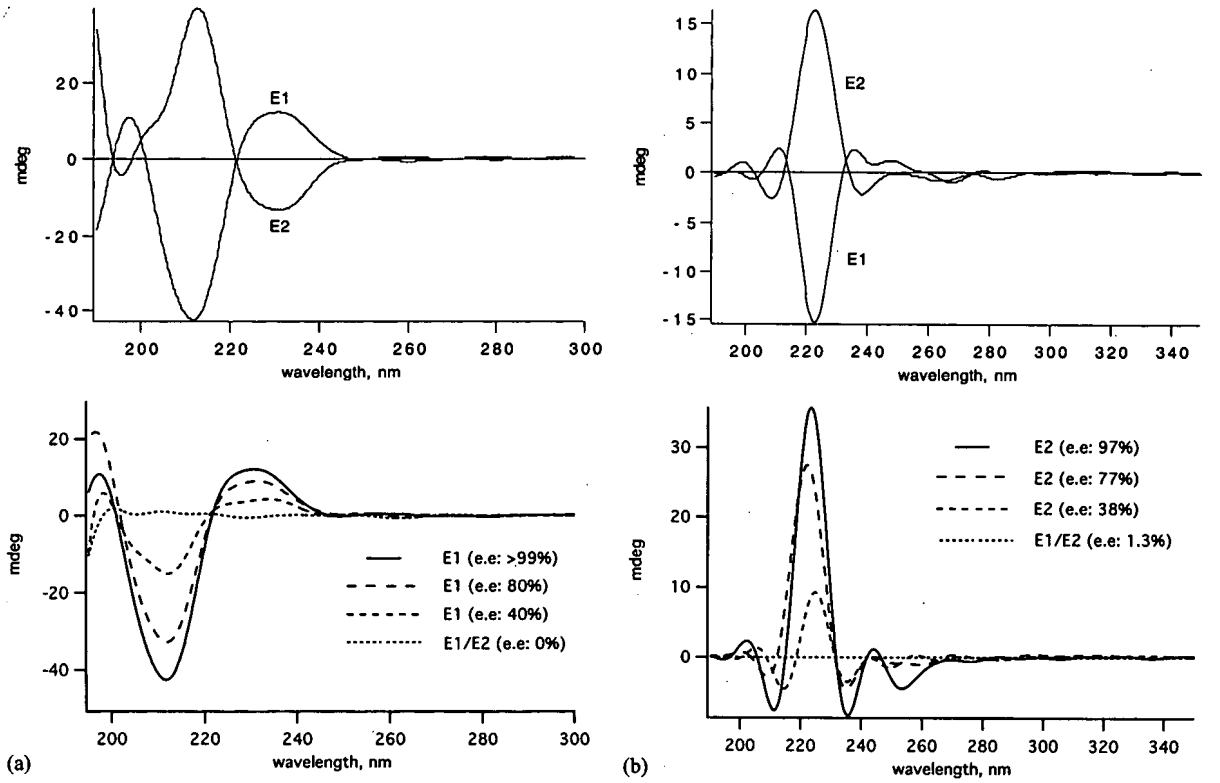

Fig. 3. The influence of enantiomeric excess on circular dicroic (CD) absorption bands, (a) CD spectra of chlorcyclizine, the isolated enantiomers (e.e. ≥ 98%) (above), at decreasing enantiomeric excess (below), (b) CD spectra of terconazole: the isolated enantiomers (above), at decreasing enantiomeric excess (below).

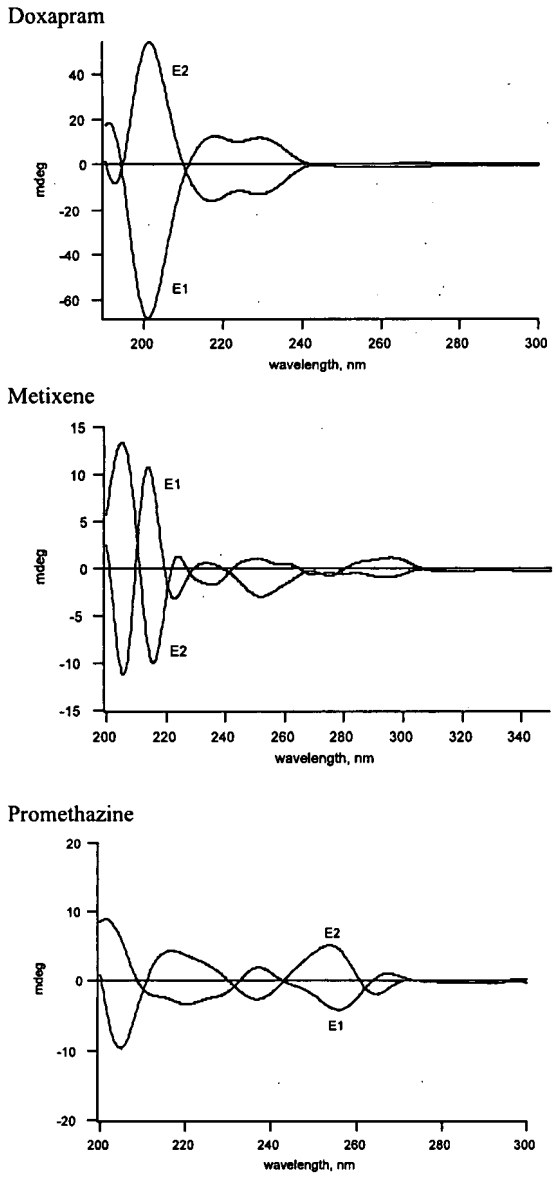

Fig. 4. CD spectra of some of the compounds studied.

Fig. 4 gives some further examples of CD spectra obtained for the compounds investigated. Metoprolol was resolved as the tartrate, but the measurements of the AoR were performed on the enantiomers of the free base. The CD spectra in Fig. 5 show that the tartrate of the metoprolol enantiomer gives a strong negative absorption band at 210 nm. Since this band is absent in the CD spectrum of the corresponding succinate, it must be caused by the optically active tartrate ion. The CD spectrum of metoprolol as the free base shows a weak negative band at 210 nm, indicating that the metoprolol has not been completely purified.

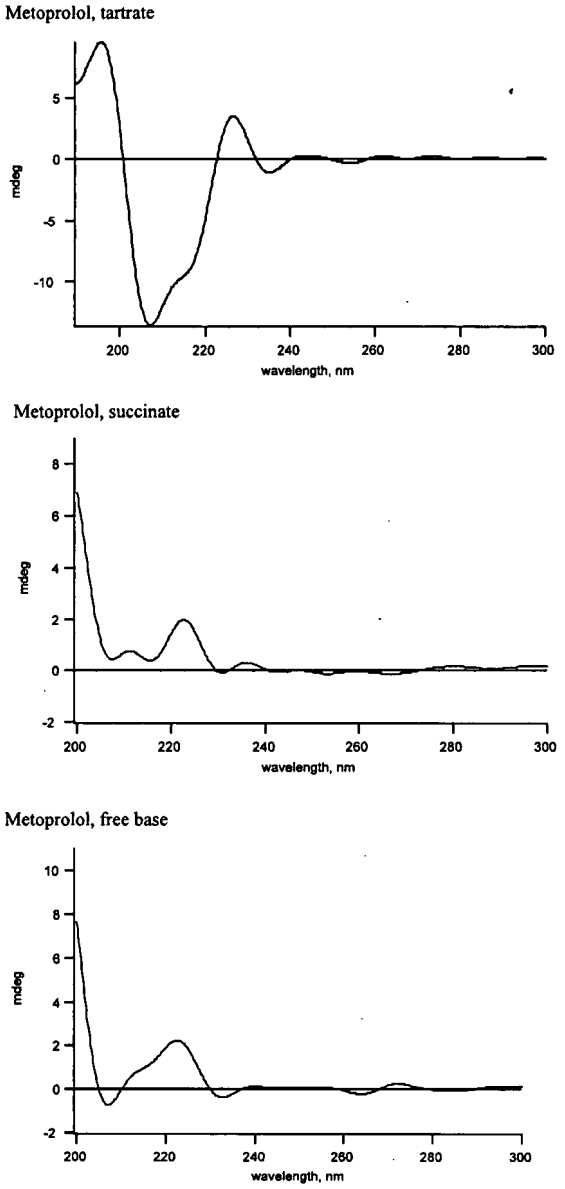

Fig. 5. CD spectra of the (+)-(R)-enantiomer of metoprolol as a salt (tartrate and succinate) and as a free base.

6. Other approaches to the analysis of chiral compounds

Due to rather weak discrimination power of AoR by polarimetry, it could be of value to consider other methods of analysis. CD spectroscopy [4,5] has been mentioned above, but at present the technique is not so widely used in the pharmaceutical control laboratories. Chiral chromatography [6] is, however, becoming more common in the pharmaceutical laboratories today and could be a real alternative. An older approach is the formation of diasteromeric derivatives, by which the racemate reacts with a chiral reagent [7,8] and is applicable in those cases where reactions are feasible.

7. Conclusions

This study has shown how to get information on the chiroptical properties of enantiomers obtained, e.g. by preparative chiral chromatography. It has also been demonstrated that polarimetry is not very sensitive to mixtures that contain the enantiomers with e.e. from 40 to 80%. This means that the use of AoR as an identification or purity test is not always particularly relevant. It has also been clearly shown that CD spectroscopy can more accurately determine the optical purity of non-racemic mixtures of a number of structurally different compounds due to higher sensitivity. CD spectroscopy or chiral chromatography should, therefore, be the technique of choice in the determination of optical purity of a chiral compound, especially for those exhibiting low AoR.

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A High-Performance Liquid Chromatographic Method for the Quantitative Enantioselective Analysis of Mefloquine Stereoisomers

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Received February 21, 1992; accepted June 22, 1992

A rapid quantitative, enantioselective HPLC method for the analysis of the four stereoisomers, (+) and (−) erythro and (+) and (−) threo forms, of mefloquine has been developed using a Chiralpak AD analytical column containing amylose tris-3,5-dimethylphenyl carbonate coated on silica gel and hexane/ethanol/diethylamine (96:4:0.1, v/v%) as the mobile phase. This method made it possible to quantitate small amounts of threo form in the presence of the erythro form of mefloquine, the form which is used as the active ingredient in commercial mefloquine tablets. Tablets from three sources were studied to estimate their optical purity, and it was found that tablets from one source contain 0.27 w/w% of the (−)-threo and 0.25 w/w% of the (+)-threo form, tablets from the second source contain 0.056 and 0.042 w/w% (−)- and (+)-threo, respectively, and tablets from the third source contain 0.052 w/w% (+)-threo, with the remainder erythro.

KEY WORDS: mefloquine; high-performance liquid chromatography; enantiomer separation; optical purity; determination in tablets.

INTRODUCTION

Mefloquine hydrochloride (Fig. 1) is a synthetic 4-quinoline methanol compound effective against chloroquine- and quinine-resistant strains of *Plasmodium falciparum*. F. I. Carroll and J. T. Blackwell synthesized four optical isomers (Fig. 2) of the compound, which chemically is α-[2,8-bis(trifluoromethyl)-4-quinolyl]-α-(2-piperidyl)-methanol hydrochloride (1). The agent is administered orally as the erythro form, that is, a racemic mixture of the (+)-(11*R*,2′*S*) and (−)-(11*S*,2′*R*) forms.

Gimenez *et al.* have reported on the resolution of two of the enantiomers of erythro mefloquine on an (*S*)-naphthylurea chiral stationary phase using a hexane–2-propanol–methanol (82:4:14, v/v) mobile phase. The stereoselectivity factor (α) was 1.63 (2). They have also employed a coupled achiral–chiral system, with chloroquine as internal standard to separate the two enantiomers in plasma and whole blood. The system they used consisted of a cyano-bonded phase and a (*S*)-naphthylurea chiral stationary phase connected by a switching valve equipped with a silica precolumn. In a pilot pharmacokinetic study performed on a single subject, the authors found that the plasma concentration of (−)-mefloquine was greater than that of the (+)-enantiomer. The (−)-mefloquine/(+)-mefloquine plasma concentration ratio varied from 1.7 at 2 hr to 11.5 at 504 hr. They also reported that both the absorption and the elimination of the drug are stereospecific (2). In an earlier *in vitro* study, Ngiam and Go demonstrated that (−)-mefloquine is a more potent inhibitor of acetylcholinesterase and butyrylcholinesterase than (+)-mefloquine. However, no reports have appeared concerning the therapeutic usefulness or toxicity of threo mefloquine. Therefore, it seems reasonable to expect that compendial standards developed for this drug product will include a measurement of enantiomeric purity, since some stereoisomers could potentially exhibit toxic effects.

We have developed a rapid, quantitative, enantioselective HPLC method for the analysis of the four stereoisomers of mefloquine.

MATERIALS AND METHODS

Reagents and Chemicals

Erythro and threo racemates and four stereoisomers of mefloquine hydrochloride were characterized products supplied by the Walter Reed Army Institute of Research. One lot of tablets (Lot E598) was obtained from the same source and had been manufactured by a generic firm. These tablets are referred to hereafter as WR tablets. Lariam (mefloquine hydrochloride; Roche) tablets (Lot 0014) were purchased from a local wholesaler. Mephaquin (mefloquine hydrochloride; Mepha) tablets (Lot 91565) were generously supplied by Mepha Ltd., Aesch-Basle, Switzerland. Hexane, ethanol, and methanol were HPLC grade; diethylamine and concentrated ammonia solution were reagent and GR grade, respectively.

Chromatographic Method

The HPLC system used consisted of a solvent delivery pump (Shimadzu LC-6A), an injection valve (Rheodyne 7161) fitted with a 20-μl loop, a variable-wavelength UV-VIS detector (Shimadzu SPD-6AV), and an integrator (Shimadzu CR-601). The detector wavelength was set at 285 nm, and the sensitivity range was 0.005–0.04 AUFS. The mobile phase consisted of hexane/ethanol/diethylamine (96:4.0:0.1%, v/v) and was filtered through an 0.50-μm filter before use. The flow rate was set at 1.0 ml/min. The HPLC column used was a Chiralpak AD analytical column containing amylose tris-3,5-dimethylphenyl carbamate coated on silica gel with a particle size of 10 μm (250 × 4.6 mm; Daicel Chemical Industries). Analyses were performed at room temperature.

Identification of Four Stereoisomers by HPLC

Ten milligrams of the hydrochloride salt of each isomer was dissolved in 10 ml of water, and 0.5 ml of ammonia solution was slowly added. The free bases obtained were filtered off, washed with water, and dried in a vacuum desiccator for 2 days. These free bases of four isomers were

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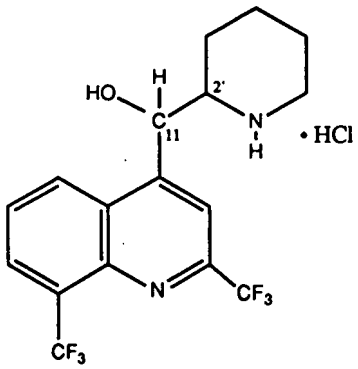


Fig. 1. Mefloquine hydrochloride.

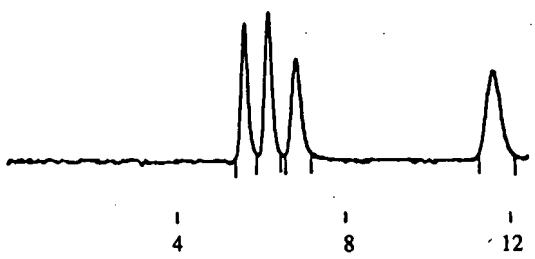


Fig. 3. Chromatogram illustrating the separation of a mixture of racemic (±)-threo and racemic (±)-erythro mefloquine. Column: Chiralpak AD (250 × 4.6 mm). Mobile phase: hexane–ethanol–diethylamine (96:4:0.1). Flow rate: 1.0 ml/min. Retention times: (+)-(11*R*/2'*R*)-threo, 5.72 min; (−)-(11*S*/2'*S*)-threo, 6.29 min; (−)-(11*S*/2'*R*)-erythro, 6.95 min; (+)-(11*R*/2'*S*)-erythro, 11.67 min.

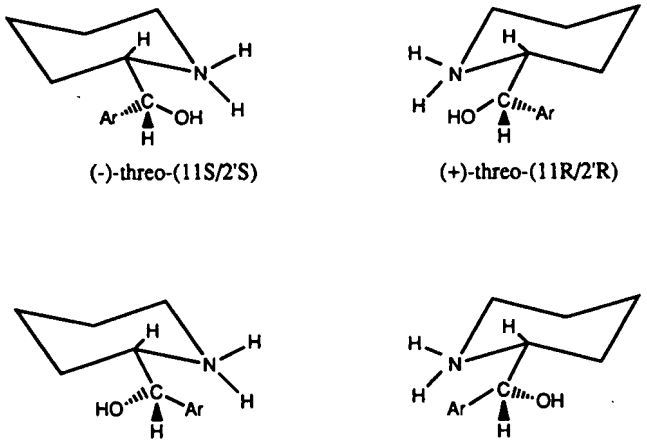
dissolved in the HPLC mobile phase and injected onto the HPLC to determine the enantiomeric elution order.

Preparation of Standard Curve

One hundred milligrams of the erythro and threo racemates of mefloquine hydrochloride was dissolved in 100 ml of water, and 5 ml of ammonia solution was added. These free bases of erythro and threo racemates were filtered off, washed with 20 ml of water, and dried in a vacuum desiccator for 2 days. Stock solutions of these erythro and threo racemates were prepared by dissolving them in the HPLC mobile phase (250 and 50 μg/ml, respectively) and dilutions were performed to obtain a series of solutions with concentrations ranging from 0.25 to 2.5 μg/ml of the threo and 5 to 50 μg/ml of the erythro form. These standard solutions were injected onto the HPLC and the standard curves for each individual isomer were obtained.

Sample Preparation for Determining the Optical Purity of Mefloquine in Commercial Tablets

Ten tablets of mefloquine hydrochloride were weighed and finely ground. Then 0.1, 0.5, or 1.0 mg of the hydrochloride salt of the threo form was added to the ground tablets, equivalent to 100 mg of the erythro form of mefloquine hydrochloride, and these mixed samples were sonicated with 50 ml of methanol for 5 min. After filtration, the filtrate was evaporated to dryness in a rotary evaporator and the residue was stored in a vacuum desiccator for 2 days. The residue was dissolved in 100 ml of water, the solution was filtered, and 5 ml of ammonia solution was added to obtain tablet free base. The precipitate was filtered, dried, washed with 20 ml of water, and dried in a vacuum desiccator for 2 days. The dried samples were used to determine the optical purity of the mefloquine hydrochloride in tablets obtained from three sources. The HPLC method described above was used for the analyses.



Ar=2,8-bis(trifluoromethyl)-4-quinolyl group

Fig. 2. Absolute configurations of four stereoisomers of mefloquine.

RESULTS AND DISCUSSION

Chiral Separation of the Four Mefloquine Isomers

In order to achieve optimum direct separation of the mefloquine stereoisomers, different concentrations of 2-propanol or of ethanol in hexane were used as the mobile phase. Since mefloquine is a secondary amine, the addition of 0.1%

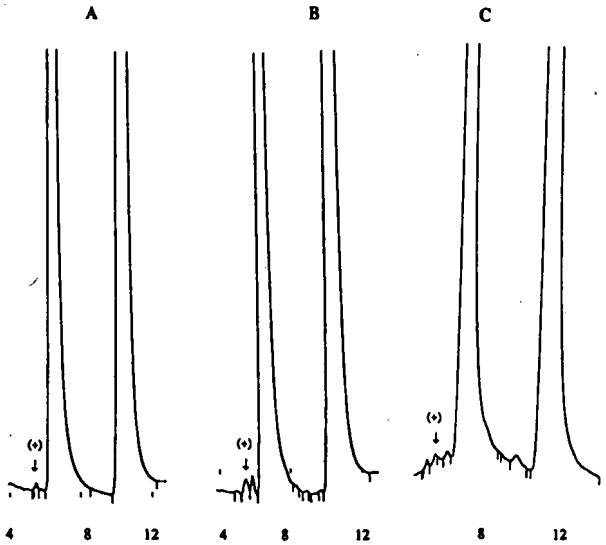


Fig. 4. Chromatograms of the samples obtained from tablets of racemic (±)-erythro mefloquine. Conditions were the same as in Fig. 3. (A) Lariam tablets. Retention times: 5.40, 6.48, and 10.39 min. (B) WR tablets: retention times—5.46, 5.84, 6.49, and 10.40 min. Mephaquin tablets: retention times—5.72, 6.40, 7.10, and 11.83 min.

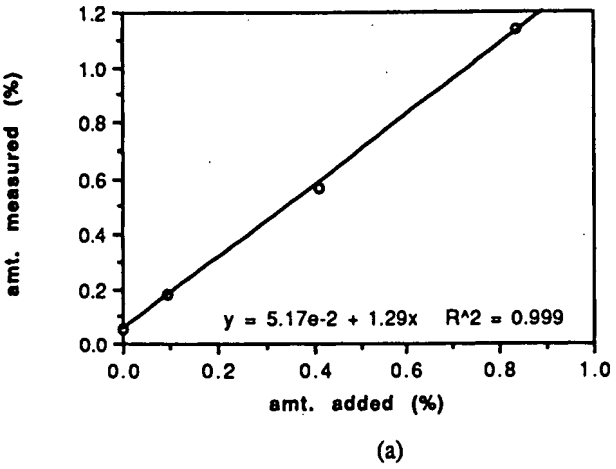


Fig. 5. Relationship between percentage added and percentage measured of mefloquine for Lariam tablets: (a) (+)-threo; (b) (−)-threo mefloquine.

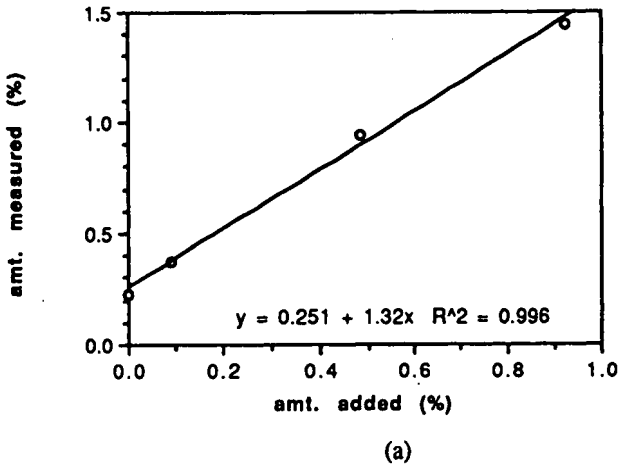


Fig. 6. Relationship between percentage added and percentage measured of mefloquine for WR tablets: (a) (+)-threo; (b) (−)-threo mefloquine.

of diethylamine was found to improve the resolution of the threo form and suppress the tailing of the elution peaks. A representative chromatogram illustrating baseline enantiomeric separation of the mixture of racemic (±)-threo and racemic (±)-erythro mefloquine is shown in Fig. 3. In the case of the threo form the peak that eluted first was identified as (+)-(11*R*/2′*R*)-threo, and the second peak that eluted was identified as (−)-(11*S*/2′*S*)-threo. Similarly for the erythro form, the peak that eluted first was (−)-(11*S*/2′*R*)-erythro and the second peak was (+)-(11*R*/2′*S*)-erythro.

As shown in Fig. 3, the four stereoisomers of mefloquine can be completely separated using the above-mentioned HPLC method.

Quantitation

Mean peak heights for each enantiomer from duplicate injections of solutions of mefloquine with six concentrations ranging from 0.25 to 2.5 μg/ml for threo and 5 to 50 μg/ml for erythro were plotted against the corresponding concentrations. Good linear relationships were obtained for each enantiomer of mefloquine. The regression equations obtained at different sensitivities were as follows.

$y = 370x - 3.73$, $R^2 =$ 0.997, $n = 6$, for (+)-threo at 0.005 AUFS.

$y = 343x - 3.26$, $R^2 =$ 0.997, $n = 6$, for (−)-threo at 0.005 AUFS.

$y = 23.7x - 8.17$, $R^2 =$ 1.000, $n = 6$, for (+)-erythro at 0.04 AUFS.

$y = 37.3x - 12.8$, $R^2 =$ 1.000, $n = 6$, for (−)-erythro at 0.04 AUFS.

It is evident that it is possible to detect and quantitate small amounts of the threo form in the presence of the predominant erythro form.

Optical Purity Determination of Commercial Tablets

Commercial mefloquine hydrochloride tablets from

three sources were studied to confirm optical purity. Figure 4 shows chromatograms of the active ingredient obtained by extraction from the tablets. Figures 5 and 6 show the relationship between added amounts of the standard threo form and measured amounts of the threo form in the active ingredient extracted from two tablet lots. Figure 4 shows that small amounts of the (+)- and (−)-threo forms were observed in the WR tablets, while it was difficult to detect peaks corresponding to the threo form in Lariam tablets. In order to determine the exact amounts of the threo form in tablets, known amounts of the threo form were added to ground material obtained from the three lots of commercial tablets. Good linear relationships between percentage added and percentage measured for threo mefloquine are observed in all cases, as shown in Figs. 5 and 6. Therefore, the impurity level of threo mefloquine in the tablets containing erythro mefloquine can be determined from the intercept of the regression equation for each enantiomer. It was found that the Lariam tablets contain 0.00 w/w% of (−)-threo and 0.052 w/w% of (+)-threo, while the WR tablets contain 0.270 w/w% of (−)-threo and 0.251 w/w% of (+)-threo mefloquine.

A similar plot (not shown) was obtained for the Mephaquin tablets, with the relationships between percentage added and percentage measured of mefloquine as follows.

(+)-Threo: $Y = 0.0417 + 1.31x$, $R^2 = 1.000$.
(−)-Threo: $Y = 0.0562 + 1.24x$, $R^2 = 0.999$.

Thus, these tablets contain 0.042 w/w% of (+)-threo and 0.056 w/w% of (−)-threo mefloquine.

CONCLUSIONS

The HPLC method described here is capable of exhibiting baseline resolution of all four isomers of mefloquine. Furthermore, this method has the advantage of being rapid and direct since it requires no derivatization and can be used for optical purity determination of the individual enantiomers in formulations as well as in pure materials. It can also provide a reliable and less tedious alternative to the chemical isolation of mefloquine enantiomers because of the availability of the Chiralpak AD preparative column.

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